VOLUME 53 NUMBER 7 JULY 1960

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of the

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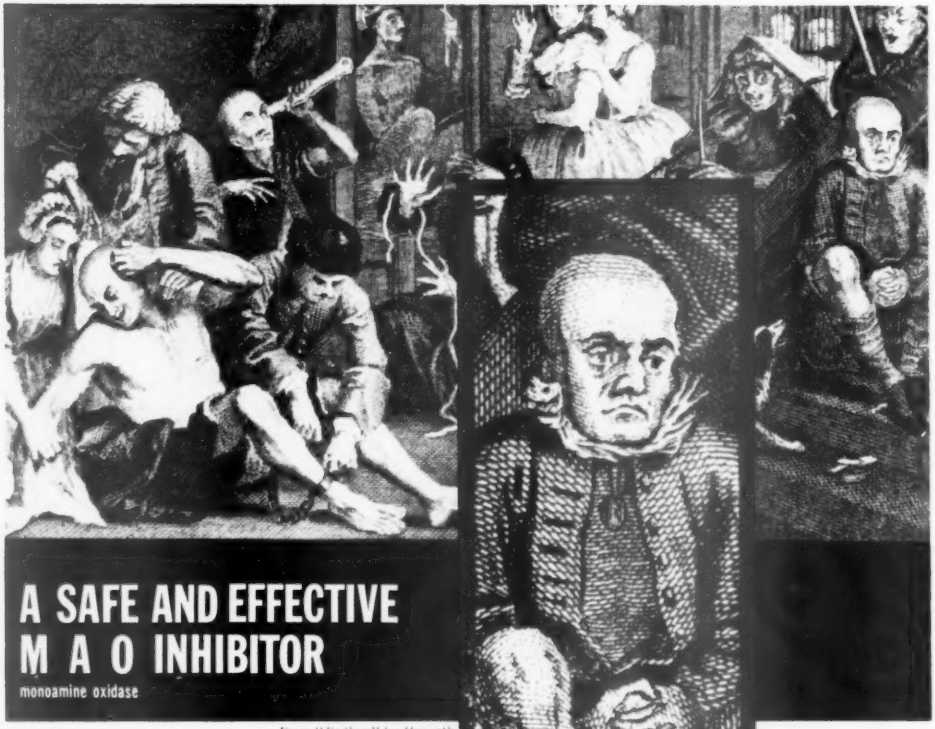

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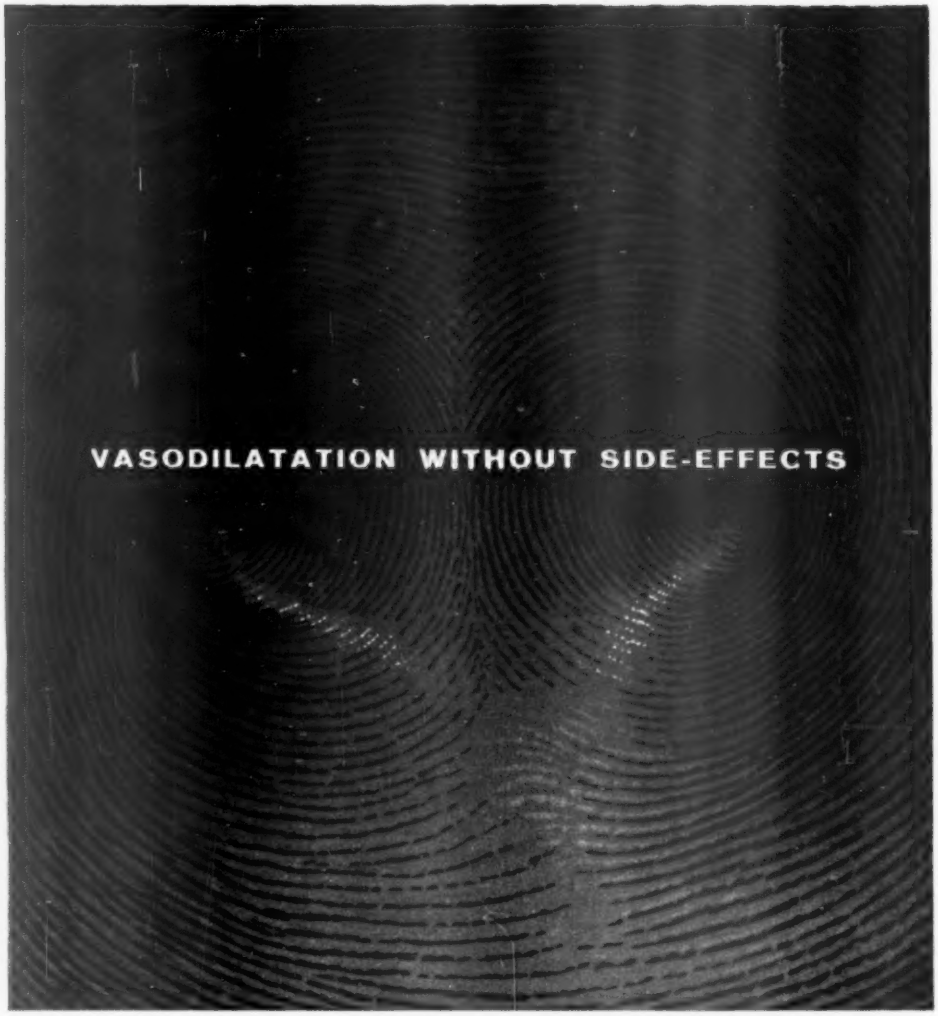

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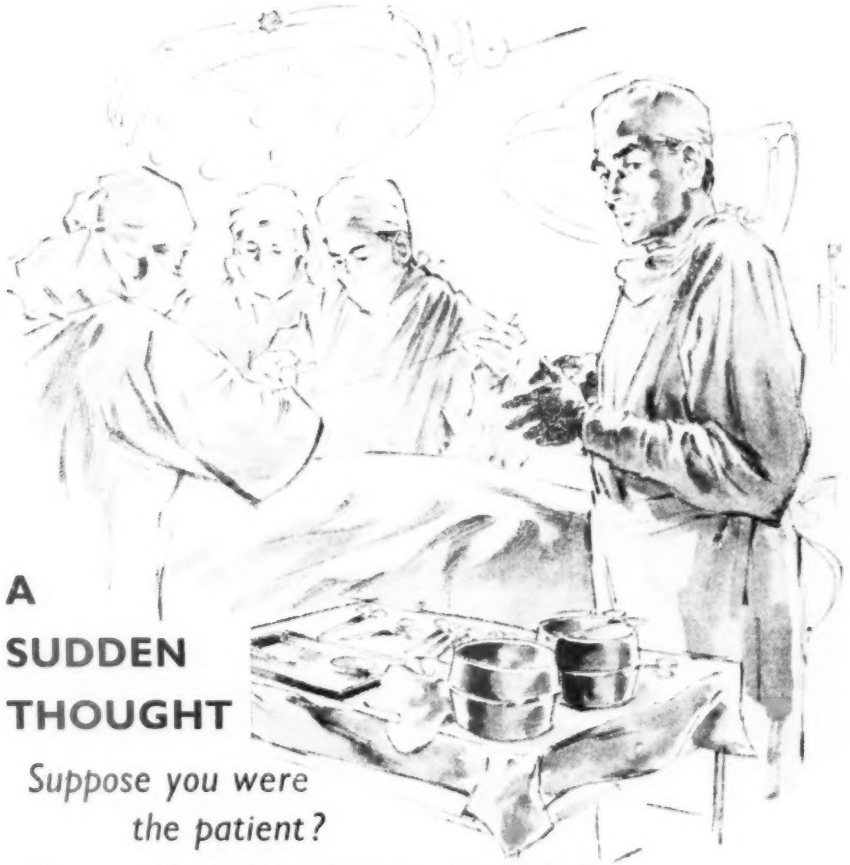

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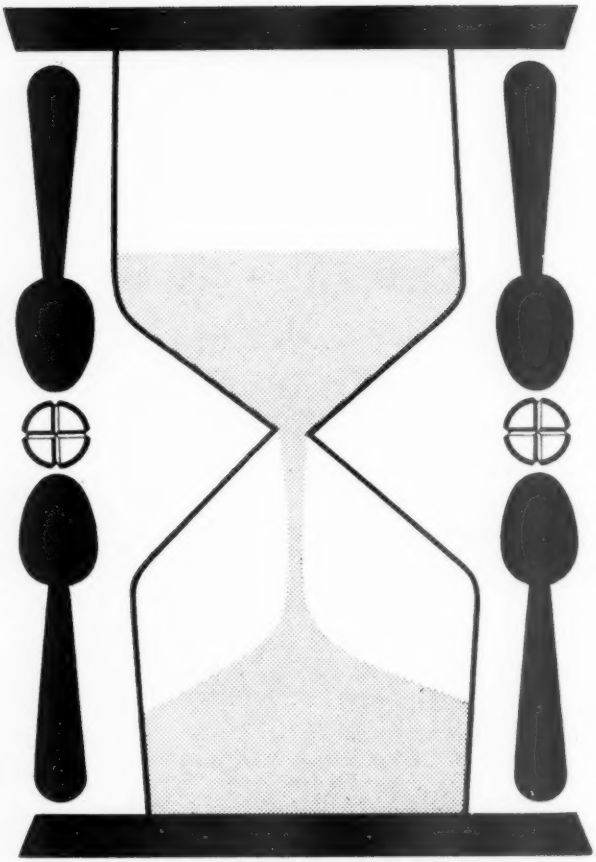

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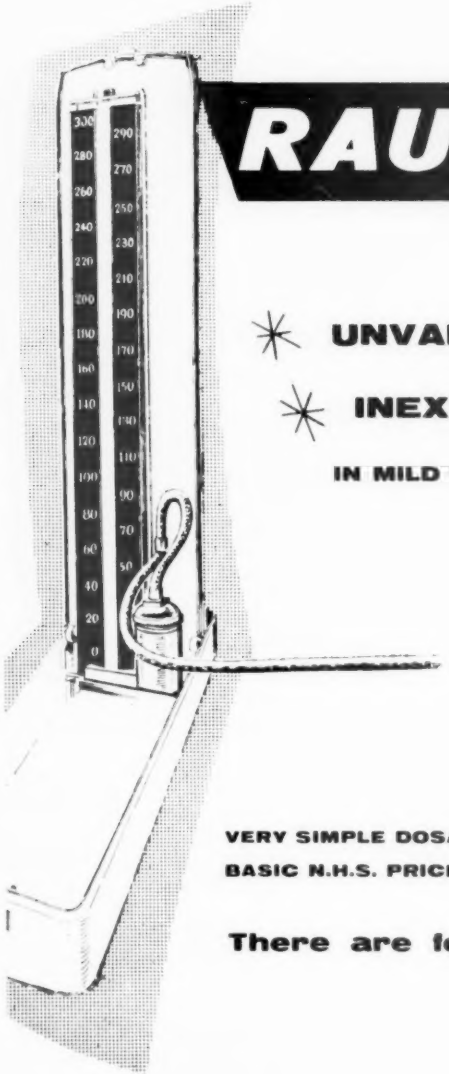

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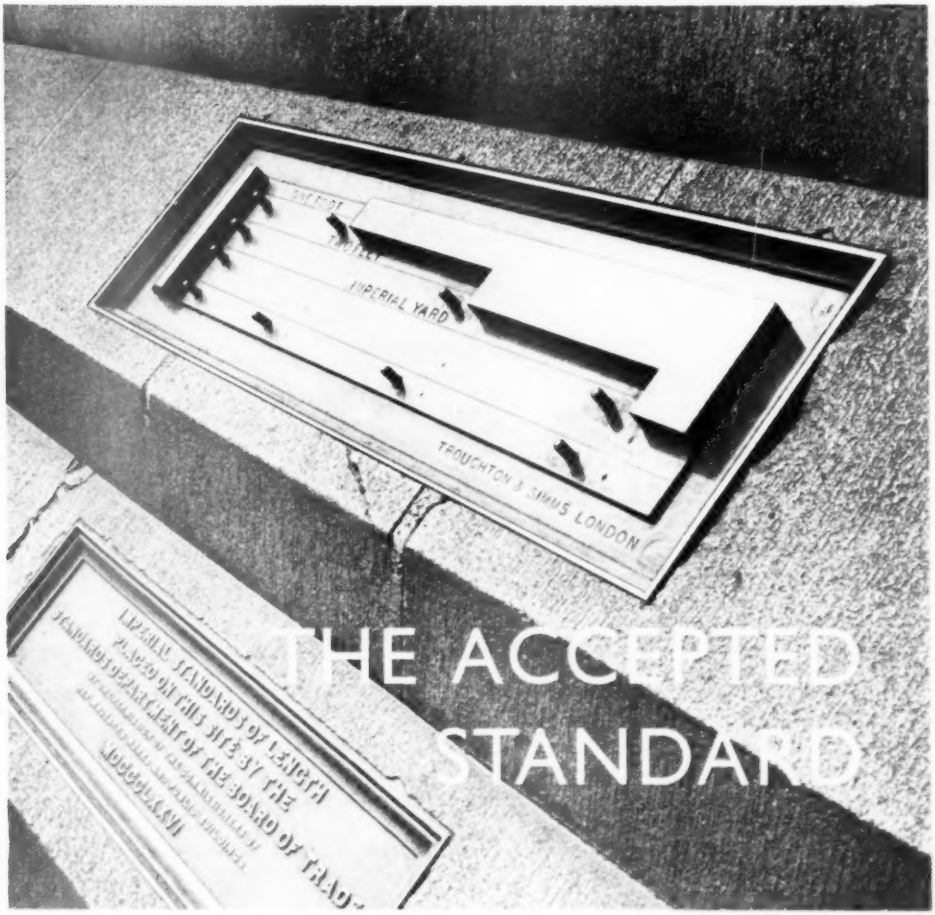

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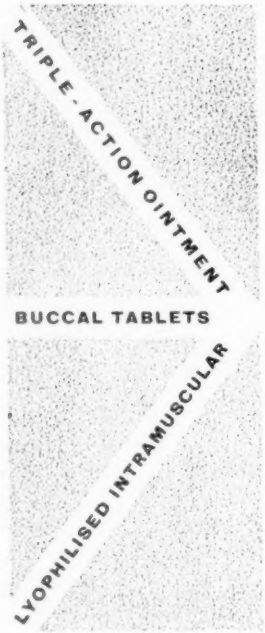

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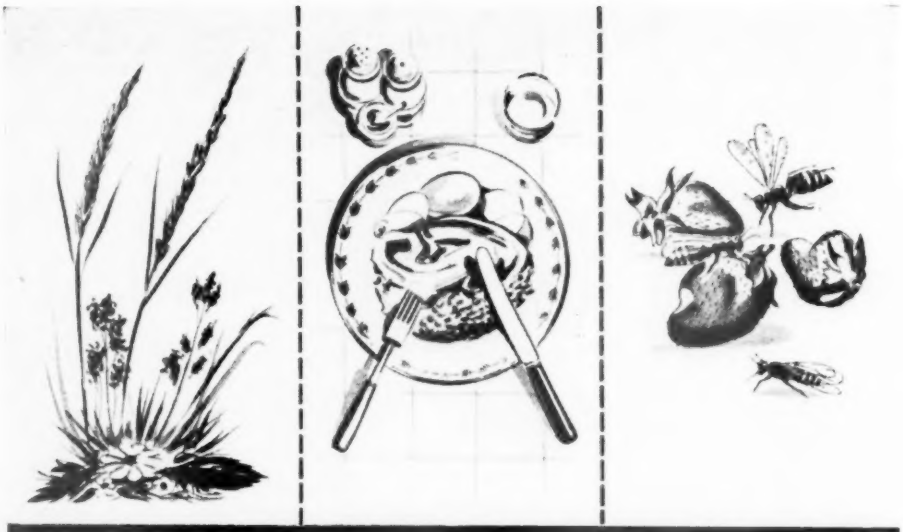

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Treatment of Congenital Hip Dysplasia in Older Children

PRESIDENT'S ADDRESS

By DAVID TREVOR, M.S.

London

HIPPOCRATES first described the clinical features of a dislocated hip in a child but gave such a gloomy prognosis that further interest was stifled; not until the beginning of the eighteenth century did an account appear by Verduc of an attempt, admittedly a failure, to reduce the dislocation. No more was heard until the middle of the century when Andry referred to the difference between birth dislocation and that due to disease: treatment he considered was useless. And so a further period of stagnation set in except for a casual reference by Paletta to a post-mortem examination in a boy of 11 with bilateral congenital dislocation of the hip. Even Dupuytren in 1826, who described the clinical features with his accustomed accuracy, decided that any treatment would be misguided: he dismissed the condition as hopeless (Hass, 1951).

But through the gloom a twinkle appeared sporadically: Pravaz in 1838 reported the first account of a successfully closed reduction obtained by several months of traction on the limb with daily manipulation of the hip in the direction of hyperextension and abduction: unfortunately the reduction was not permanent. Little further progress was made, partly by reason of late diagnosis but partly by failure to retain the reduction.

With the discovery of anæsthetics and with the past experience of inevitable re-dislocation, it is not surprising that the surgeons of that time turned their attention to "open" operative treatment. Poggi in 1888 became the first to reduce and maintain the reduction by such means: this stimulated Hoffa of Germany and Lorenz of Vienna. Enthusiasm may have outrun surgical skill, for in 1895 Lorenz proclaimed to the world his famous bloodless reduction—a method more forcible than that of Paci's which Lorenz had witnessed the previous year at the International Congress in Rome (Allison, 1928). Credit goes to Lorenz for recognizing the factors involved in successful treatment—not only reduction but retention of the dislocation. His method was not without risk: in 450 patients there were 2 deaths from shock associated with the manipulation, 13 fractures chiefly of the femur but also of the pelvis, more than 10 peripheral nerve injuries, one instance of total gangrene of the lower limb, together with many less serious traumatic effects (Davis, 1904). No wonder that less forceful methods were sought until at present closed reduction is effected by gentle gradual means.

But even with gentler procedures, the results of the closed method of treatment leave much to be desired. The long-term results of many reasonably sized series of patients are depressing: it is evident that the earlier the age at which treatment is instituted, the higher will be the percentage of favourable results of conservative treatment. Putti (1929) appreciated this and proclaimed that if all patients were diagnosed and treated in early infancy the problem of congenital dislocation of the hip would be virtually solved. He viewed the condition purely as one of displacement of the femoral head, the reduction of which would stimulate the development of the acetabulum. This does occur, but unfortunately is by no means invariable.

More recently a new conception has appeared (Hart, 1942): no longer is the condition considered primarily a dislocation with a defective socket development as its result. In fœtal life some factor, which may be genetic, mechanical or constitutional, singularly or collectively, interferes with the natural growth of the hip-joint, producing a dysplastic condition. If the disturbance is minimal, a minor blemish results which may disappear spontaneously; a greater disturbance produces a major blemish with perhaps prenatal dislocation. Dysplasia is characterized by retardation of ossification of cartilage causing a sloping osseous acetabular roof, a wider gap of unossified cartilage than normally between the ischial and pubic rami, delayed appearance of, or a small ossific femoral head nucleus (Fig. 1). Anteversion and valgus deformity of the femoral neck may be a primary abnormality according to Badgley (1943) but there is much evidence to suggest that it is a secondary manifestation.

Cartilage has not the same resistance to pres-

FIG. 1.—Features of dysplasia of the left hip: poorly developed acetabular osseous roof, wide gap between the osseous part of the pubis and the ischium, small ossific femoral nucleus and displacement of the femur.

sure as bone: thus, in spite of a well-developed cartilaginous roof, if the osseous part is defective, the upward thrust of the femoral head will meet with less resistance than normally with a possible resultant subluxation or dislocation: we are then dealing with a complication of the dysplasia. Where the influence of the dysplastic process is minimal, little abnormal anatomy occurs. Under such circumstances spontaneous correction is possible; at the worst, abduction of the hip generally produces full correction. But without treatment, the anatomy becomes increasingly abnormal with the continued effects of the dysplasia so that a subluxation or dislocation occurs before the child walks. Frequently the dysplastic element is such that subluxation may not occur until after the age of 3 years, and there may be cases where subluxation may not be noticed until early adult life when symptoms are manifest for the first time. The hips may not be equally affected: often in a unilateral subluxation or dislocation the opposite, allegedly normal, hip shows radiologically some evidence of dysplasia: this is important, for such a hip should be immobilized so that it cannot adduct while the affected hip is being treated. Should the dysplastic hip adduct, the influence of the dysplasia on the acetabular roof increases, allowing a silent subluxation or possibly a dislocation to occur. Scaglietti maintains that birth dysplasia is always bilateral and spontaneous healing of the less affected side can occur, leaving a unilateral affection (Hass, 1951).

The cause of the dysplasia is unknown: it exerts its influence from the pre-natal period: with successful treatment its influence may cease: on the contrary, even with apparently successful initial treatment and particularly in unsuccessful treatment, its effect may continue unabated until skeletal growth ceases.

The child over 3 years of age with a subluxed or dislocated hip is often a real orthopædic problem, on account of the greater defect of hip development as well as the soft-tissue changes secondary to walking on an unstable hip. For the younger child, conservative measures must be employed initially, and surgery carried out only when failure occurs or seems imminent—a decision which should be made early in the treatment. In the older child conservative treatment can succeed (Fig. 2) but unfortunately in only a small minority; generally some type of operative procedure is necessary for the management of these older children. Age alone does not determine

FIG. 2A.—Child over 3 on first attendance for treatment.

FIG. 2B.—Treated conservatively throughout.

the actual procedure employed, but rather the age and the intensity of the dysplasia.

100 hip "operations" in patients over 3 years of age are analysed in Table I and the type of operation employed in these 100 consecutive hips in Table II.

TABLE I—100 HIP "OPERATIONS" AT AGES ABOVE 3 YEARS

100	61 (Previous treatment)	26 (re-dislocations)
		35 (subluxations)
	39 (No previous treatment)	22 (dislocations)
		17 (subluxations)

TABLE II—OPERATIONS ON 100 HIPS (SINGULARLY OR IN COMBINATION)

Reduction	Open replacement, 35
	Capsular arthroplasty, 13
Retention	Acetabuloplasty, 68
	Shelf, 7
	Osteotomy, 54
Obliteration	Arthrodesis, 4 (including 1 capsular arthroplasty)

Operative Findings in Open Replacement of the Femoral Head

In all but 5, a thickened deformed capsule in response to weight bearing on an unstable hip formed the main obstacle to the head entering the acetabulum: with upward displacement of the femur, the lower part of the capsule screens the lower half or more of the plane of the socket, the opening to which is often narrowed by indentation by the psoas tendon leading to the lesser trochanter (Fig. 3); further, the inner side of the upper part of the capsular hood is adherent to the ilium above the acetabulum—thus between the upper and lower capsular margins there exists a narrow, often slit-like, opening, much too small for the passage of the femoral head, generally just sufficient to allow the ligamentum teres, when present, to proceed to the floor of the acetabulum. The guiding principle to achieve replacement without any force was one of adequate soft-tissue dissection—wide excision of the capsule, removal of the ligamentum teres and of all soft tissue from the acetabulum, and division of the psoas tendon and adductor tenotomy when necessary (Table III).

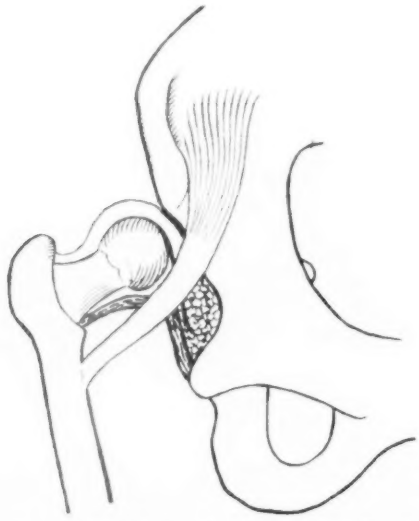


FIG. 3.—Secondary soft tissue changes found at operation in older children.

TABLE III—FINDINGS AT 35 OPEN REPLACEMENT OPERATIONS

Main cause of obstruction:
- Thick adherent capsule 30
- Enlarged ligamentum teres .. 3
- Obliteration of socket by tissue .. 2

Psoas tendon divided 15 (Twice combined with adductor tenotomy)

Ligamentum teres: Absent 9 Bifid 5

Femoral head deformed 20
Ovoid 12. Hemispherical 5. Enlarged radial head 1. Nodular and lozenged shaped 1. Poorly developed 1.

Eroded 17 (Complete adherency to capsule 1)

Anteversion varied from 30–120 degrees

Acetabular deformity: Mostly shallow with triangular shape: 1 funnel shaped.

The ligamentum teres, when present, aided the location of the acetabular fossa frequently obscured by soft tissue: often it was absent, occasionally bifid and in a bilateral lesion fared differently on each side. When present it was removed but no evidence of blood vessels either macroscopically or microscopically was found. In three instances it was unnaturally large and was the chief barrier to reduction.

Somerville (1953) has laid stress on the presence of an enlarged inverted limbus (i.e. cotyloid ligament) as an important agent in preventing concentric reduction in young children. In older children the limbus played only a minor role but in two instances the whole mouth of the acetabulum was occupied by a thick, resistant, fibrocartilaginous diaphragm similar in appearance to a discoid semilunar cartilage.

Deformity of the femoral head was encountered in over half the open replacement operations: the normal spherical head was replaced by an ovoid, a hemi-spherical head with flattening on the medial or posterior aspect, a lozenge-shaped or an enlarged head similar to an enlarged radial head. Erosion of the articular cartilage occurred in slightly less than 50% and it was noted that erosion was more likely to be encountered where the hip had been subjected to previous treatment, particularly repeated manipulations. Deformed heads were not necessarily eroded and vice versa.

The acetabular fossa seemed shallow in all instances: the degree of shallowness varied: occasionally the fossa was funnel shaped rather than triangular. The fossa was occupied by loose soft tissue which was easily removed, even with gauze dissection, revealing the horseshoe-shaped articular cartilage which presented no

evidence of erosion as distinct from that of the femoral head.

Post-operatively, the hip was immobilized in a plaster of Paris spica: a position of a few degrees of abduction in all instances, with full internal rotation in most, was that of greatest stability. In no instance was the position of external rotation found to be stable. The position of internal rotation indicated a degree of anteversion which was corrected by a subtrochanteric osteotomy combined with a varus wedge resection when a valgus femoral neck deformity was present. At first plaster of Paris immobilization was continued for twelve weeks, but now the period has been reduced to an average of nine weeks. After this period the child is allowed to kick around in the bed: he should lie prone for part of the day and should sleep in this position at night if possible in order to minimize the danger of a flexion deformity at the hip: should this occur immediate skin traction to the limb will be necessary for its correction. The aid of the physiotherapist is invoked as soon as the plaster spica has been removed so that the child may regain as full a function of the hip as soon as possible. While the child is active in bed, but not yet allowed to walk, assisted hip exercises, particularly extension and abduction, are started; later the same exercises are carried out against resistance. Only when reasonable function is obtained, generally in three to four weeks, is the child allowed first to exercise in the pool and finally to walk, at first assisted. This post-immobilization treatment does nothing towards the anatomical result which is accomplished at operation and which should be definitive unless the influence of dysplasia continues, as it unfortunately does in many instances.

In a bilateral case one hip is dealt with at a time (Fig. 4).

Capsular Arthroplasty

Capsular arthroplasty was first suggested by Hey Groves (1928). Later Colonna (1932) modified his method and has written extensively on the subject so that the operation is known by his name. The procedure is normally performed in two stages: first an adequate pre-operative skin or skeletal limb traction extending over several weeks, combined with immobilization of the opposite hip in a plaster of Paris spica if necessary. If this preliminary traction is faithfully carried out the making of the new socket at the operation (second stage) at the level of the original acetabulum becomes easier. If the socket is made too high an unsightly limp results: if made at the right level without traction, difficulty may be experienced in reducing the head, while excessive pressure on such a reduced head may cause aseptic avascular necrosis.

The essential steps of the second stage are:

(*a*) Dissection of the muscles off the capsule and division of the hour-glass constriction when persent so that the femoral head is completely covered by capsule which is lined with synovial membrane and yet the capsule-covered femoral head is free from any attachment to the acetabulum.

(*b*) The production of an adequately deepened cup-shaped (not saucer-shaped) socket as near the natural acetabulum as possible: demonstration of the Y-shaped cartilage is an important landmark as regards level. To deepen the new socket it is permissible to penetrate the pelvic wall pushing the cortical wall inwards (Fig. 5).

(*c*) The capsule-covered femoral head is reduced without force into the newly furnished socket: the capsule eventually becomes adherent to the raw bone while the femoral head moves inside the synovial lined capsule. The socket must be large enough to take the capsule-covered femoral head: on no account must the head be made smaller.

Up to the age of 6 years open replacement is possible and preferable to the capsular arthroplasty, but if the femoral head is too large for the acetabulum (this being determined if necessary by arthrograms) or if the acetabulum is very poorly developed and irregular, the dysplasia affecting chiefly the acetabulum while the femoral head has a reasonable shape, then capsular arthroplasty is indicated (Fig. 6). After the age of 6 years, open replacement can only be accomplished with dangerous pressure on the femoral head: under these circumstances the arthroplasty procedure is strongly indicated, particularly so in a unilateral rather than in a bilateral condition.

In the first 100 hip operations, the selection as outlined above was not followed rigidly: some hips then dealt with would be discarded now. This I believe accounts for many of the inferior results compared with those of open replacement.

The post-operative regime is similar to that of open replacement but mobilisation is much slower and passive internal rotation exercises of the hip were needed.

Acetabuloplasty

Many surgeons have doubted the value of acetabuloplasty, maintaining that with concentric reduction of the femoral head the development of the acetabulum including its roof will be stimulated and that all will be well. This does occur as can be demonstrated mathematically by a gradual reduction in the C.E. angle (Wiberg, 1939). Unfortunately it is not invariable even in the very young child, due undoubtedly to the

FIG. 4A.—Bilateral dislocation at age 3½.

FIG. 4B.—Open replacement, acetabuloplasty and rotation osteotomy of each hip.

FIG. 4C.—Three years later: Plate and screws used for the osteotomy have been removed.

FIG. 5B.—X-ray appearance after capsular arthroplasty. The socket is at the same level as the original; the pelvic wall of the new acetabulum has been pushed inwards to make for increased depth. Rotation osteotomy has been performed. →

FIG. 5A.—Congenital dislocation of hip in child aged 6.

FIG. 6A.—Poorly developed acetabulum. Well-shaped femoral head, as determined by arthrogram. An ideal case for capsular arthroplasty.

FIG. 6B.—Unwisely an acetabuloplasty was performed, the head remaining in an eccentric position. Capsular arthroplasty (Colonna's operation) would probably have produced a better result.

FIG. 7A.—Child aged 4. Subluxation as a result of a dysplastic hip.

FIG. 7B.—Acetabuloplasty. The roof is turned down over the concentrically reduced head.

continued influence of the dysplasia. It must be admitted that its need in the young is infrequent and only required when open replacement is unstable due to a shallow roof: under these circumstances no apology is necessary; there may be regrets if the procedure is omitted. But in the older child conditions are different; the dysplastic effects have lasted longer so that there is an appreciable lag in the ossification of the cartilage of the acetabular roof: replacement of the head after 3 years of age under such circumstances hardly ever allows a natural speed up of roof ossification so that the potential danger of redislocation is very real, a danger which is increased should there be uncorrected femoral neck deformity—anteversion and/or valgus—with an unnatural thrust against the poorly resisting cartilaginous roof.

← FIG. 8A.—Subluxation of hip-joint due to (1) sloping osseous acetabular roof and (2) ante-version with valgus deformity of the femoral neck.

FIG. 8B.—Correction of femoral neck deformity, subsequent to acetabuloplasty, by rotation osteotomy with varus wedge resection on account of valgus deformity. The correction has been overdone: although the hip is stable, its function could have been considerably better had the wedge taken from the inner side of the femoral shaft been less. →

FIG. 9A.—Showing congenital dislocation of the hip, which, after closed reduction, redislocated.

FIG. 9B.—Ten months later: First-stage acetabuloplasty.

←FIG. 9C.—Acetabuloplasty completed by second stage after an interval of two weeks. Rotation osteotomy was also performed.

FIG. 9D.—Intermediate result after 2½ years. →

← FIG. 10A.—Subluxation in a child 10 years of age.

FIG. 10B.—Shelf operation performed with the head now in a concentric position. It is unwise to place a shelf over a subluxated or dislocated femoral head. →

Acetabuloplasty is an extra-articular procedure whereby the roof is turned over a concentrically placed femoral head in a swing fashion, the fulcrum being at a point on the inner pelvic wall just above the acetabulum; it should extend from just above the anterior margin right back to the posterior margin towards the sciatic notch and should be deep enough to penetrate the pelvic wall in order to produce a full swing downwards (Fig. 7). An extension of this procedure has been recommended by Chiari (1955) of Vienna who divides the whole ilium high up and displaces this portion of bone outwards over the femoral head which may be placed eccentrically. Anatol (1959) of Tel Aviv combines with this a division of the os pubis and ischium, maintaining that it is easier to move the acetabulum and place it over a displaced femoral head than to place the femoral head into an acetabulum which is defective and possibly itself displaced.

The gap above the acetabulum resultant on turning the roof downwards is filled with bone, either autogenous from the iliac crest or homogenous from a bone bank. Post-operative immobilization in a full hip spica plaster of Paris or by continuous traction on a hip frame is maintained for eight weeks. Framed traction should be better, for the head can be kept from pressing on the roof, but plaster of Paris immobilization works well and is easier for nursing. Any femoral neck deformity should be corrected at the same time but can be deferred if necessary for two to three weeks (Fig. 8).

Mobilization of the hip is carried out on exactly similar lines as after open replacement.

Occasionally the acetabulum is so shallow, i.e. high C.E. angle, that acetabuloplasty should be abandoned in favour of a capsular arthroplasty later at a suitable time; it is possible however to overcome the difficulty of this extreme shallowness by performing a second-stage operation: at the first operation a mass of bone is placed in the region of the final acetabuloplasty which is effected at the second stage (Fig. 9).

In 100 hips dealt with over three years, acetabuloplasty was necessary in 68, either alone or generally combined with other procedures such as open replacement or osteotomy. There is an upper age limit, for after 8 years the bone is not sufficiently pliable to turn down easily: it is then probably better to do a formal shelf operation, which essentially is the insertion of bone into the ilium as near the acetabular roof as possible to extend the roof laterally: there is no question of prising the roof downwards (Fig. 10).

The purpose of the acetabuloplasty is stability without restriction of movement: this was obtained in nearly all instances but in 12 hips absorption of bone graft occurred, necessitating a further operation. In one instance osteochondritic changes occurred in the acetabulum with very considerable stiffness—a failure. Of the 12 cases of absorbed acetabuloplasty, iliac bone alone had been used in 7, while only one occurred with bone bank, when a rather inadequate amount had been employed. It seems that cancellous tissue has not the same resistance against pressure as the more cortical bone bank of ribs; a mixture of iliac and bone bank proved the most satisfactory. Other causes of the absorption were technical errors, such as turning down too thick a roof, placing the bone graft too high, and failure to correct deformity of the femoral neck with resultant unnatural head pressure on the roof (Table IV).

Osteochondritis or epiphysitis of the femoral nucleus is a real bugbear: its actual cause is unknown; many explanations have been ad-

TABLE IV.—CAUSES OF ABSORPTION OF ACETABULOPLASTY (12 CASES) (SINGULARLY OR IN COMBINATION)

Use of iliac bone alone	7
Insufficient bone used	2
Insertion of bone too high	2
Failure to penetrate the inner pelvic wall	2
Failure to correct femoral neck deformity	6
Accepting an eccentric position of femoral head	2

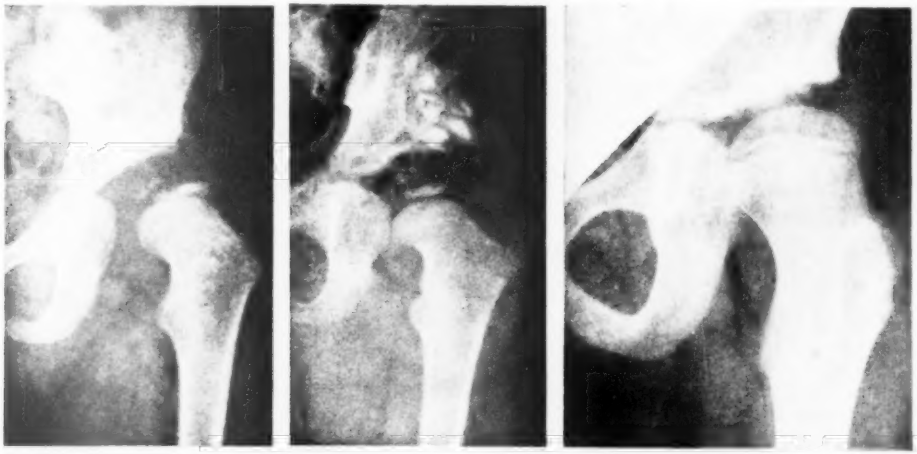
vanced. It is generally assumed that interference with the vascular supply is responsible; some authorities have suggested that attenuation of the ligamentum teres with its blood supply may be a factor. At operation no evidence of bleeding was seen when the ligamentum was excised nor any microscopic evidence subsequently; invariably the ligamentum was excised when present and yet the incidence of epiphysitis was less than with closed means. No method of treatment has been published to date which eliminates this complication; forcible means, such as manipulative reduction, produce a higher percentage (one-third of all cases) than the more gentle and gradual means of reduction, e.g. frame traction followed by plaster of Paris fixation. It can occur after the very simple treatment of immobilizing the hip in abduction; it has been observed in the normal hip while both hips were immobilized in abduction on account of an alleged unilateral dysplasia. As all dysplastic hip-joints do not develop the complications, the method of reduction can only be an added factor, important though it is. The aplastic nucleus in subluxed or dislocated hips is part of the dysplasia with, in many instances, a precarious blood supply: so that even a minimum of force is sufficient to tip the balance. A factor fairly common to all methods is the position of wide abduction; may not this position obliterate the inferior capsular vessels so that the precarious blood supply suffers further, particularly when, as commonly occurs, the adductor muscles are taut? I would suggest that before the abducted position is obtained, even gradually, subcutaneous adductor tenotomy with long axis traction be employed for about two weeks. This may diminish the incidence of epiphysitis still further.

A minor degree of epiphysitis does not influence greatly the long-term results, but a more pronounced degree may mar the result (Table V).

TABLE V.—EPIPHYSITIS (OSTEOCHONDRITIS) POST-OPERATIVELY (7 CASES): INTERMEDIATE RESULTS

Open replacement	2	1 excellent, 1 good
Capsular arthroplasty	3	2 good, 1 fair
Acetabuloplasty	2	1 good, 1 fair (in one hip changes of epiphysitis in the femoral nucleus and acetabular roof)

In the past insufficient attention has been paid to its treatment. No weight-bearing should be allowed, and even when the period of hip immobilization has ceased the child should thereafter walk on a weight-relieving caliper with a patten on the opposite shoe, until the ossific nucleus has reformed. Should a subluxation occur in the presence of the epiphysitis due to a defective osseous acetabular roof or persistent femoral neck deformity, or both, the appropriate operative procedure should be undertaken unhesitatingly (Figs. 11 and 12).



A B C

FIG. 11.—A, Subluxation after closed reduction due to sloping roof; epiphysitis of the femoral head; B, Acetabuloplasty performed; C, The acetabular roof has moulded well and the ossific nucleus has reformed comparatively well. The femoral head is still slightly higher than normal.

FIG. 12A.—Subluxation due, in this instance, largely to anteversion. There is an epiphysitis of the femoral head.

FIG. 12B.—After rotation osteotomy. The femoral head has formed reasonably well and is in normal relationship with the acetabulum. →

Intermediate Results

End results of congenital dysplasia of the hip can only be supplied at the end of the patient's ambulatory life; this is ideal but rather impracticable. The long-term results can only be supplied by our successors; this emphasizes the need to record accurately the method of treatment so that they may judge its efficiency or otherwise. I can only present intermediate results, some over twelve years (Table VI).

TABLE VI.—INTERMEDIATE RESULTS (BASED ON MULLER AND SEDDON'S METHOD)

	Excellent	Good	Fair	Poor	Total
1. *Hips*	44	34	18	4	100
2. *Operations*					
Open replacement	16	15	4	—	35
Capsular arthroplasty	1	2	9	—	12
Acetabuloplasty or shelf	33	32	9	—	74
Rotation osteotomy alone with/without varus wedge resection	6	1	—	—	7
Arthrodesis	—	—	—	4	4

The assessment, by Mr. Ian MacKenzie, has been based on Muller and Seddon's method (1953) which was modified from that suggested by Buxton; it has the advantage that the anatomical state of the hip as well as its function is considered, for a hip with excellent function but anatomically defective is not likely to retain such function into early adult life.

To quote from Hey Groves (1928): "In concluding this short account of the operative treatment of congenital dislocation of the hip, I can only express the firm conviction that all cases of this deformity are amenable to cure or alleviation. Although it is quite true that if all cases came for diagnosis and treatment in early infancy there would be little need for open operation, yet this ideal is probably a long way off, and in the meantime I am sure that there is no justification for the common attitude of pessimism about the cases older than three to four years, most of which can be cured or relieved."

[Two films were shown: one demonstrated the essential steps in the operative procedures employed, and the other some representative intermediate results.]

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REFERENCES

ALLISON, N. (1928) The Robert Jones Birthday Volume. London; p. 97.

ANATOL, A. (1959) Personal communication.

BADGLEY, C. E. (1943) *J. Bone Jt. Surg.*, **25**, 503.

CHIARI, K. (1955) *Z. Orthopäd.*, **87**, 14.

COLONNA, P. C. (1932) *J. Bone Jt. Surg.*, **14**, 277.

DAVIS, G. G. (1904) *Amer. J. orthop. Surg.*, **1**, 266.

GROVES, E. W. H. (1928) The Robert Jones Birthday Volume. London; p. 73.

HART, V. (1942) *J. Bone Jt. Surg.*, **24**, 753.

HASS, J. (1951) Congenital Dislocation of Hips. Springfield, Ill.

MULLER, G. M., and SEDDON, H. J. (1953) *J. Bone Jt. Surg.*, **35B**, 342.

PUTTI, V. (1929) *J. Bone Jt. Surg.*, **11**, 798.

SCAGLIETTI, O. Quoted by Haas (1951) p. 42.

SOMERVILLE, E. W. (1953) *J. Bone Jt. Surg.*, **35B**, 363.

WIBERG, G. (1939) *Acta chir. scand.*, **83**, Suppl. 58.

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FIG. 12A.—Subluxation due, in this instance, largely to anteversion. There is an epiphysitis of the femoral head.

FIG. 12B.—After rotation osteotomy. The femoral head has formed reasonably well and is in normal relationship with the acetabulum. →

Intermediate Results

End results of congenital dysplasia of the hip can only be supplied at the end of the patient's ambulatory life; this is ideal but rather impracticable. The long-term results can only be supplied by our successors; this emphasizes the need to record accurately the method of treatment so that they may judge its efficiency or otherwise. I can only present intermediate results, some over twelve years (Table VI).

TABLE VI.—INTERMEDIATE RESULTS (BASED ON MULLER AND SEDDON'S METHOD)

	Excellent	Good	Fair	Poor	Total
1. *Hips*	44	34	18	4	100
2. *Operations*:					
Open replacement	16	15	4	—	35
Capsular arthroplasty	1	2	9	—	12
Acetabuloplasty or shelf	33	32	9	—	74
Rotation osteotomy alone with/without varus wedge resection	6	1	—	—	7
Arthrodesis	—	—	—	4	4

The assessment, by Mr. Ian MacKenzie, has been based on Muller and Seddon's method (1953) which was modified from that suggested by Buxton; it has the advantage that the anatomical state of the hip as well as its function is considered, for a hip with excellent function but anatomically defective is not likely to retain such function into early adult life.

To quote from Hey Groves (1928): "In concluding this short account of the operative treatment of congenital dislocation of the hip, I can only express the firm conviction that all cases of this deformity are amenable to cure or alleviation. Although it is quite true that if all cases came for diagnosis and treatment in early infancy there would be little need for open operation, yet this ideal is probably a long way off, and in the meantime I am sure that there is no justification for the common attitude of pessimism about the cases older than three to four years, most of which can be cured or relieved."

[Two films were shown: one demonstrated the essential steps in the operative procedures employed, and the other some representative intermediate results.]

Acknowledgments.—I am grateful to my colleagues at the Royal National Orthopædic Hospital and elsewhere for their kindness in referring patients; to Miss P. Turnbull for making lantern slides, and to Mr. J. R. Whitley of the Photographic Department of the Institute of Orthopædics, Royal National Orthopædic Hospital, for the cine films.

REFERENCES

ALLISON, N. (1928) The Robert Jones Birthday Volume. London; p. 97.

ANATOL, A. (1959) Personal communication.

BADGLEY, C. E. (1943) *J. Bone Jt. Surg.*, **25**, 503.

CHIARI, K. (1955) *Z. Orthopäd.*, **87**, 14.

COLONNA, P. C. (1932) *J. Bone Jt. Surg.*, **14**, 277.

DAVIS, G. G. (1904) *Amer. J. orthop. Surg.*, **1**, 266.

GROVES, E. W. H. (1928) The Robert Jones Birthday Volume. London; p. 73.

HART, V. (1942) *J. Bone Jt. Surg.*, **24**, 753.

HASS, J. (1951) Congenital Dislocation of Hips. Springfield, Ill.

MULLER, G. M., and SEDDON, H. J. (1953) *J. Bone Jt. Surg.*, **35B**, 342.

PUTTI, V. (1929) *J. Bone Jt. Surg.*, **11**, 798.

SCAGLIETTI, O. Quoted by Haas (1951) p. 42.

SOMERVILLE, E. W. (1953) *J. Bone Jt. Surg.*, **35B**, 363.

WIBERG, G. (1939) *Acta chir. scand.*, **83**, Suppl. 58.

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Meeting
December 8, 1959

The Chromosomes of Normal Human Somatic and Leukæmic Cells
[*Abridged*]

By C. E. Ford, B.Sc., Ph.D.

Harwell

In the last few years new techniques have brought about a considerable increase in our knowledge of human chromosomes. The chromosomes in natural mitotic (and meiotic) divisions are crowded on top of one another and are only resolved as separate structures by very careful technical processing and the most painstaking microscopy. The main object of the new methods was therefore to disperse the chromosomes widely within the cytoplasm of the dividing cell so that counts and observations of detailed morphology could be made easily and accurately. Three main kinds of material have been used: tissue cultures, suspensions of bone marrow cells, and seminiferous tubules—the ultimate source of all being biopsy specimens.[1]

The normal number of chromosomes in human somatic cells is 46 in both sexes (Tjio and Levan, 1956). At the first meiotic division in primary spermatocytes the 46 chromosomes form 22 symmetrical (autosomal) pairs and one unequal pair (the sex chromosome pair, XY) (Ford and Hamerton, 1956). In somatic cells the two separate members of some of these pairs can be recognized as individual chromosomes; other pairs are more difficult to distinguish and it is convenient to classify them into similar groups of 4 or 6. The Y chromosome is commonly identifiable as a separate chromosome but the X chromosome(s) cannot yet be distinguished with certainty from the members of a similar autosome pair. In the female this pair and the X chromosome pair are the sixth and seventh in order of relative length. At mitotic metaphase the longest and shortest chromosomes are about 7μ and 1μ long respectively. Each chromosome is divided into two arms by the centromere, which may be median or submedian (metacentric chromosomes), or nearly terminal (acrocentric chromosomes). Centromere position and relative length are the two principal features used for the identification of individual chromosomes. (*See* Ford, 1960, for a more extensive summary of recent developments in human cytogenetics.)

Until recently it was commonly asserted that the number of chromosomes in mammalian somatic tissues was variable (Beatty, 1954). Were this so it would have indicated that normal metabolism of a tissue cell was not dependent upon the presence of a normal complement of chromosomes. Furthermore no special importance could be attached to the reports of variation of chromosome numbers in neoplastic tissue. Change from disorder to somewhat greater disorder does not suggest itself as being of fundamental significance. Use of the newer techniques, however, indicates that there is in fact a high degree of constancy of chromosome number in mammalian somatic tissues (Walker and Boothroyd, 1954; Hungerford, 1955). In reticular tissues of the mouse, for instance, the frequency of cells with abnormal chromosome numbers (polyploid cells being excluded) has been estimated to be no greater than 0·4% (Ford, Hamerton and Mole, 1958). There is as yet no corresponding estimate for man, but counts made on the best bone-marrow preparations from otherwise healthy patients with congenital abnormalities suggest a similar value.

It has been known for a long time that mitotic irregularities are frequent in neoplastic tissues and that the cells often contain abnormal numbers of chromosomes. The earlier observations, however, were rather imprecise and more recent work suggests that some essential features had been obscured. Studies of transplanted ascites tumours of the mouse and the rat by Makino and his associates in Japan provided the first

[1]Tissue cultures can sometimes be established successfully from specimens taken at autopsy.

indication that some degree of order might underlie the apparent chaos of variation. The observations suggested that the main bulk of the tumour was perpetuated by normal mitotic division of a particular cell-type, the "stem-line", from which the variant cells arose as abnormalities (Makino, 1956; Levan, 1956). Examination of an extensive series of primary and transplanted reticular neoplasms ("leukæmias") of the mouse indicated that the same generalization held true for them also (Ford and Mole, 1959). Most of these neoplasms were characterized by a modal cell-type with a chromosome set that differed from the normal set of the species either in number, or morphology, or both. In almost all there was some variation around the modal number (in contrast to the near constancy in somatic tissues), and in several of them instances of primary structural change in the chromosomes gave evidence of the origin of morphologically new chromosome types. In a few neoplasms the modal chromosome set was so highly individual as to provide a secure means of identification in transplanted lines.

Recognition of the high frequency of "chromosomal abnormality" in these murine "leukæmias" prompted Dr. R. H. Mole and myself to attempt to get preparations from human leukæmic cells. Injection of colchicine (or Colcemid) into the mouse shortly before sacrifice had been an essential part of the technique. Since injection of these drugs into the human patient before sternal biopsy was inadmissible, trials were made in which fresh sternal biopsy specimens were incubated in the presence of one of them. This simple approach was unsatisfactory. An alternative was offered by the short-term culture method for bone-marrow suspensions developed by Dr. L. G. Lajtha, and with his help the method was successfully adapted for chromosome studies. Initially there was difficulty in getting enough cells to enter mitosis in the suspensions established from leukæmic patients, and sufficient observations to be useful were obtained only from 3 out of the first 12 that were examined. In 2 of these no abnormality was detected. The third was strikingly different: most cells contained 45 chromosomes only, including a very small fragment; there was some variation in the count, and also a subsidiary mode at 90 chromosomes including two identical small fragments (Ford, Jacobs and Lajtha, 1958).

Subsequently, Drs. Lajtha, C. M. Clarke and I examined the chromosomes in incubated marrow suspensions from further leukæmic patients, and we now have information from 10 cases. 6 of these were blast-cell leukæmias of which 4 exhibited distinctive chromosome changes. No decisive evidence of abnormality was observed in 2 cases of chronic myeloid leukæmia and in 2 cases of chronic lymphatic leukæmia. These results are in accord with recently published findings of the M.R.C. Group in Edinburgh (Baikie *et al.*, 1959).

The case examined most recently (one of the six blast-cell leukæmias) deserves special mention. Counts obtained from a sternal biopsy showed a pronounced bimodal distribution with one mode at 46 and another, minor mode at 48. The preparations were of good quality and 8 cells were analysed in detail. These revealed that the 46-chromosome cells contained an apparently normal set, and that the 48-chromosome cells had a normal set with two *constant* extras, one being a small acrocentric chromosome difficult to separate from the Y, and the other a medium length metacentric chromosome. A week after the sternal puncture a suspension was set up from peripheral blood and processed in the same way as bone-marrow. Again the same two modes were observed but the one with a mode at 48 had become dominant.

Unfortunately, the peripheral blood preparations were not good enough to permit a detailed analysis of the morphology of the individual chromosomes. Nevertheless the cells with 48 chromosomes may be considered to be leukæmic cells. It is also reasonable to suppose that many if not all of the 46-chromosome cells in the marrow were normal (i.e. non-leukæmic) cells. But the 46-chromosome cells in the peripheral blood pose a problem. Dr. Lajtha informs me that it would be most unusual to find cells capable of mitosis in the peripheral blood of a normal individual. Nevertheless in the leukæmic patient this possibility cannot be excluded. We are faced with the alternatives of two separate leukæmic cell-populations, or the presence in the blood of both leukæmic *and* normal cells capable of undergoing mitosis. In any case the evidence points to the presence of a population of leukæmic cells with a highly individual chromosome set.

So far as they go, the observations on the chromosomes of human leukæmic cells are in agreement with those made on the reticular neoplasms and ascites tumours of the mouse and rat. Those cases in which no abnormality was detected could be of three types: cases that involve chromosome change but in which the abnormality is below the level of resolution by present methods; cases in which the leukæmic cells have normal genotypes and chromosome sets; and cases in which the dividing leukæmic cells were, for some reason, not represented among the cells observed.

The rodent and human data together are con-

sistent with the concept of a neoplasm as a genotypically mixed, but still highly individual, population of cells, in which new genotypic variation is continuously arising, thereby providing a basis for selective proliferation of different cell lines and progressive change in the properties of the neoplasm as a whole. This concept has the advantage of providing a ready explanation of neoplastic individuality and adaptation, as well as of progression, and is essentially that put forward by Winge in 1930. Many more observations will be required before it can be said whether it is generally applicable, or whether it is appropriate only to certain individual neoplasms, or classes of neoplasms; and whether it is primary (and in that sense "causal"), or secondary.

REFERENCES

Baikie, A. G., Court Brown, W. M., Jacobs, P. A., and Milne, J. S. (1959) *Lancet*, ii, 425.

Beatty, R. A. (1954) *Int. Rev. Cytol.*, **3**, 177.

Ford, C. E. (1960) *Amer. J. hum. Genet.*, **12**, 104.

——— and Hamerton, J. L. (1956) *Nature, Lond.*, **178**, 1020.

———, ———, and Mole, R. H. (1958) *J. cell comp. Physiol.*, **52**, Suppl. 1, 235.

———, Jacobs, P. A., and Lajtha, L. G. (1958) *Nature, Lond.*, **181**, 1565.

———, and Mole, R. H. (1959) *Progr. nuclear Energy* (ser. VI. *Biol. Sci.*) **2**, 11.

Hungerford, D. A. (1955) *J. Morph.*, **97**, 497.

Levan, A. (1956) *Ann. N.Y. Acad. Sci.*, **63**, 774.

Makino, S. (1956) *Ann. N.Y. Acad. Sci.*, **63**, 818.

Tjio, J. H., and Levan, A. (1956) *Hereditas, Lund*, **42**, 1.

Walker, B. E., and Boothroyd, E. R. (1954) *Genetics*, **39**, 210.

Winge, Ö. (1930) *Z. Zellforsch.*, **10**, 683.

Abnormalities of Chromosome Constitution and Defects of Sex Development [*Abridged*]

By D. G. Harnden, B.Sc., Ph.D.

Edinburgh

Before the recent development of techniques for chromosome examination two methods were available for determining the genetic sex of a patient. Firstly, a small chromatin-positive body could be demonstrated in the nuclei of a proportion of cells of females but not in those of males (Barr and Bertram, 1949); secondly, "drumstick shaped" projections were to be found on a small number of the nuclei of polymorphonuclear leucocytes of females but these were never found in males (Davidson and Smith, 1954). These techniques disclosed two anomalies. Some patients with Klinefelter's syndrome were found to be chromatin positive and some patients with Turner's syndrome and all cases of testicular feminization were found to be chromatin negative. These were all considered to be cases of sex reversal.

Following the demonstration in 1956 that the normal human chromosome number is 46 (Tjio and Levan, 1956; Ford and Hamerton, 1956) several techniques have been evolved for chromosome analysis. These all involve the culture of tissue cells *in vitro;* the fixation of these cells in an actively dividing state, usually after dividing cells have been accumulated by treatment with colchicine; and the flattening of the cells by manual squashing or air drying to spread the chromosomes so that they can be readily examined. The first method widely used employed a short-term culture of bone-marrow cells (Ford *et al.*, 1958). Several different methods have been described for utilizing cell cultures established from solid tissues (Tjio and Puck, 1958; Chu and Giles, 1959; Lejeune *et al.*, 1959; Harnden, 1960). A technique for making chromosome preparations from peripheral blood has recently been described by Hungerford *et al.* (1959). Each of these techniques has its own special merits and they may be most usefully employed in conjunction with each other.

The human chromosomes can be arranged as 22 pairs of autosomes and one pair of sex chromosomes which are alike and designated XX in the female and unlike and designated XY in the male.

Chromatin-positive cases of Klinefelter's syndrome have been shown to have 47 chromosomes, there being two X chromosomes as well as one Y (Jacobs and Strong, 1959; Ford, Polani, Briggs and Bishop, 1959; Harnden, 1960). It is probable that the presence of the extra chromosome is due to a nondisjunctional error during gametogenesis in one of the parents. Theoretically Klinefelter's syndrome can arise as a result of nondisjunction in either the male or the female. There is some evidence to suggest that there is a correlation between the incidence of this syndrome and maternal age, although this is not nearly so marked as it is in the case of mongolism (Penrose, 1959). As these patients are phenotypic males it can be inferred that the human Y chromosome has a masculinizing effect (cf. *Drosophila* where the XXY individual is an infertile female).

Patients with Turner's syndrome are phenotypic females usually with primary amenorrhœa and a variety of congenital abnormalities which may include webbing of the neck. They may be chromatin positive or chromatin negative. Some

chromatin-negative cases have been shown to have only 45 chromosomes and an XO sex chromosome constitution (Ford, Jones, Polani, de Almeida and Briggs, 1959; Tjio and Puck, 1958; Fraccaro *et al.*, 1959). Ford (1960) has, however, found both XO and XX cells in some patients with Turner's syndrome and these are therefore interpreted as mosaics, i.e. made up of two kinds of cell of different genetic constitution. Turner's syndrome may also arise as a result of nondisjunction in either the male or the female parent. Study of sex linked characters such as colour blindness may suggest in which parent the defect has occurred (Stern, 1959). Mosaics, however, can be explained by an error of cell division occurring at some stage after fertilization.

Jacobs, Baikie, Court Brown, MacGregor, Maclean and Harnden (1959) have described one patient with secondary amenorrhœa, infantile genitalia and poor development of the secondary sex characteristics. This patient was shown to have two chromatin bodies in many of the cells of the buccal mucosa and 47 chromosomes in both bone-marrow and skin cells. The extra chromosome is in the same size range as the X chromosome. This evidence strongly suggests that the patient is a "superfemale" analogous to the XXX superfemale *Drosophila*.

Other abnormalities of sex chromosome constitution can arise as a result of nondisjunction during gametogenesis in the parents. Some of these, such as YO are probably inviable and others, if viable, will be very rare, but such combinations as XXXY and XYY may be found.

There are several other types of intersexuality where the number of chromosomes is normal but the phenotypic sex does not agree with the chromosomal sex. Patients with the testicular feminization syndrome are phenotypic females but are chromatin negative and have testes. Jacobs, Baikie, Court Brown, Forrest, Roy, Stewart and Lennox (1959) have examined 4 such cases and all have a chromosome constitution indistinguishable from that of a normal male. This can only mean that although sex determination is normal for a male, sex differentiation is not.

Cases of pure gonadal dysgenesis may be either chromatin positive or chromatin negative. They are all phenotypic females with primary amenorrhœa but without the usual stigmata of Turner's syndrome. Harnden and Stewart (1959) have recently reported a chromatin-negative case of this syndrome to have 46 chromosomes indistinguishable from those of a normal male. In such cases it seems that where failure of gonadal development occurs at a very early stage the development of the phenotype is in the female direction rather than in the male, regardless of the chromosomal constitution (cf. Jost's experiments with artificial castration of rabbits, 1953).

Two true hermaphrodites with both ovarian and testicular tissues have been examined and found to have 46 chromosomes and sex chromosomes indistinguishable from those of a normal female (Hungerford *et al.*, 1959; Harnden and Armstrong, 1959). This suggests that even after sex has been determined at fertilization other factors, which may also be genetically determined, profoundly influence the course of sex differentiation.

It would be wrong to believe that all these types of human intersexuality fall into clearly defined categories. It would be more advantageous to think in terms of ranges of abnormality. For example an individual arising as an XY zygote may vary from a normal male to something almost indistinguishable from a normal female. Chromosome studies, in conjunction with developmental, endocrinological and other studies may help to clarify this complex problem.

REFERENCES

Barr, M. L., and Bertram, E. G. (1949) *Nature, Lond.*, **163,** 676.

Chu, E. H. Y., and Giles, N. H. (1959) *Amer. J. hum. Genet.*, **11,** 63.

Davidson, W. M., and Smith, D. R. (1954) *Brit. med. J.*, ii, 6.

Ford, C. E. (1960) *Amer. J. hum. Genet.*, **12,** 104.

——, and Hamerton, J. L. (1956) *Nature, Lond.*, **178,** 1020.

——, Jacobs, P. A., and Lajtha, L. G. (1958) *Nature, Lond.*, **181,** 1565.

——, Jones, K. W., Polani, P. E., de Almeida, J. C., and Briggs, J. H. (1959) *Lancet*, i, 711.

——, Polani, P. E., Briggs, J. H., and Bishop, P. M. F. (1959) *Nature, Lond.*, **183,** 1030.

Fraccaro, M., Kaijser, K., and Lindsten, J. (1959) *Lancet*, i, 886.

Harnden, D. G. (1960) *Brit. J. exp. Path.*, **41,** 31.

——, and Armstrong, C. N. (1959) *Brit. med. J.*, ii, 1287.

——, and Stewart, J. S. S. (1959) *Brit. med. J.*, ii, 1285.

Hungerford, D. A., Donnelly, A. J., Nowell, P. C., and Beck, S. (1959) *Amer. J. hum. Genet.*, **11,** 215.

Jacobs, P. A., Baikie, A. G., Court Brown, W. M., Forrest, H., Roy, J. R., Stewart, J. S. S., and Lennox, B. (1959) *Lancet*, ii, 591.

——, ——, ——, MacGregor, T. N., Maclean, N., and Harnden, D. G. (1959) *Lancet*, ii, 423.

——, and Strong, J. A. (1959) *Nature, Lond.*, **183,** 302.

Jost, A. (1953) *Recent Progr. Hormone Res.*, **8,** 379.

Lejeune, J., Turpin, R., and Gautier, M. (1959) *Extr. Ann. Génét.*, **1,** 41.

Penrose, L. S. (1959) at conference on Human Chromosomes, King's College Hospital, London.

Stern, C. (1959) *Nature, Lond.*, **183,** 1452.

Tjio, J. H., and Levan, A. (1956) *Hereditas, Lund.* **42,** 1.

——, and Puck, T. T. (1958) *Proc. nat. Acad. Sci., Wash.*, **44,** 1228.

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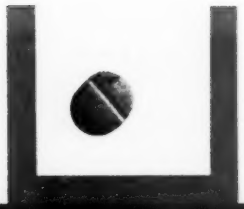

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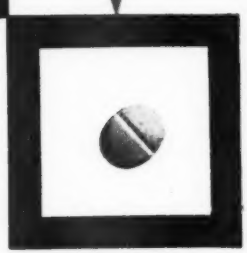

Section of Psychiatry

President—R. STRÖM-OLSEN, M.D.

Meeting
December 8, 1959

A SYMPOSIUM on **Salt and Water Metabolism in Relation to Psychiatry** was held when the following papers were read:

The Role of Electrolytes in Nervous Mechanisms.—Dr. R. H. ADRIAN.

The Sensitivity of Isolated Cerebral Tissues to Salts and Water of Their Environment, as Indicated by Metabolic and Electrical Measurements.—Professor H. MCILWAIN.

Some Clinico-Neurophysiological Problems.—Dr. G. PAMPIGLIONE.

Malnutrition and the Central Nervous System.—Professor B. S. PLATT. *See* PLATT, B. S. (1960) In: Chemical Pathology of the Nervous System. Ed. J. Polch-Pi. London (in press). PLATT, B. S., and STEWART, R. J. C. (1960) *Proc. Nutr. Soc.* (in press).

Sodium Potassium Metabolism and its Relation to Psychiatry.—Dr. J. DAWSON.

Alteration in the Rate of Entry of ^{24}Na from Blood to C.S.F. in Depressive Illness.—Dr. A. J. COPPEN.

Brain Activity and Salt and Hormone Metabolism in Recurrent Mental Disorders.—Dr. J. H. REY. *See* REY, J. H. (1957) In: Schizophrenia, Somatic Aspects. Ed. D. Richter. London.

The subsequent discussion was opened by Dr. D. RICHTER.

Meeting
January 12, 1960

Conditioning Theories and Their Therapeutic Applications

By W. GREY WALTER, M.A., Sc.D.

Bristol

SINCE, as a physiologist, I can have no direct concern with the treatment of clinical conditions, I propose to deal mainly with certain aspects of conditioning as embodied in a particular operational or working hypothesis that I developed some years ago to clear my own mind. This hypothesis is sufficiently detailed to be considered in terms of neuro-physiological mechanism, and it generates a number of practical implications and predictions; I shall describe later how my colleagues and I are trying to test these by experiments with human subjects.

My personal interest in conditioning as a physiological concept began about twenty-five years ago when, under the guidance of I. P. Pavlov and Sir Joseph Barcroft, I found myself working with one of Pavlov's pupils, J. S. Rosenthal, in Cambridge on the problem of respiratory stress and conditioning in dogs. This was a formidable problem in those days; now, when even the sky is not the limit, such experiments are commonplace, though some of them are literally above our heads.

Our aim in these experiments was to find out how hypoxia and carbon dioxide administration affected the establishment and maintenance of a variety of conditioned reflexes in five dogs. Three of these had been brought from Leningrad, two were from our own kennels. I well remember my scorn when Rosenthal, after playing with the two Cambridge dogs, said dogmatically: "This dog weak type nervous system; this dog strong choleric type." To me, as an academic physiologist, a dog was a dog, not a personality—but I soon learned better, for it was the idiosyncrasies of our creatures that finally brought the carefully planned investigation to a sterile end.

The experimental arrangement was quite traditional. There were several pairs of conditional (CS) and unconditional (UCS) stimuli, all to be accompanied by the noise of the fans and impellers for ventilating the chamber and changing the atmosphere—these were followed by neither reward nor punishment, but acted as powerful novel stimuli evoking persistent orienting reflexes. Our protocols showed that in seclusion and tranquillity with an orderly presentation of CS and UCS, all the dogs

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showed conditional responses (CR), of varying magnitude but reasonable stability, after about six trials of each combination. Considering only eighteen presentations with six pairings of each set we could arrange the associations in the form of a contingency table as if they were the observations of the dogs and the responses indicated *their* hypotheses of significance about our actions. The numbers are rather too small to satisfy a statistician but the x^2 value is very high and the odds against such a series of events occurring in this pattern are over 10,000 to one. The dogs judged rightly that the CS were worth responding to.

When the noise of the ventilating machinery was introduced the dogs had a much more difficult problem. This was further complicated inadvertently for the animals because of my misunderstanding of Russian and technical overconfidence. The situation involved twenty-five trials with 75 stimuli, but in a sense all the presentations were anomalous either in association or sequence. However, the contingency table, which can be said to represent the situation over this period from the dogs' standpoint, gives the same value of x^2 and anti-chance odds as for the smaller number of unequivocal presentations. The anomalies and irregularities may be regarded as "noise"-like exceptions to natural laws or experimental error and thus as stresses to the contingency computing mechanisms in the animals' brains. If the dogs had all been identical, one would have expected the outcome on this occasion to have been the same as before, but it was not. Only one dog, the one Rosenthal described as "sanguine," retained a reasonable repertoire of responses; of the others the two phlegmatic types became inert and indifferent, one, the choleric dog, became agitated and hostile and the melancholic dog developed an intractable and fatal neurosis. Only one creature appreciated that our plan was reasonable.

This experience was my practical introduction to the Pavlovian typology, of which we heard very little more until the last two or three years when it was salvaged from the wreck of authoritarian Soviet biology. It is worth considering in detail the basis of this schematization of temperamental difference, because it provides as it were a clinical entry to the domain of experimental physiology. Pavlov's classification was established by the identification of what we should call three "operational parameters". These are scales by which certain observable characters of behaviour can be ranked or measured; the names given to them are matters of taste and convenience—if one were considering say, chemical elements they might be density, hardness and colour. Pavlov chose to use terms that may be translated as Strength, Balance and Versatility. The relation between these parameters is suggested in Fig. 1; they can be thought of as enclosing an operational space of temperament within which the behavioural range of an individual must lie. Now, if the ratings of all individuals on these scales were normally distributed (as for example height, IQ, and EEG alpha frequency) then the dots, representing each individual's temperamental position, would cluster around the centre of the cube. Pavlov's typology is based on the observation that in the case of the dogs that he studied the temperamental positions *did not* cluster in the centre of the cube, but rather in the corners of it. This is indicated in the diagram and the representative positions of the four Hippocratic types he described are indicated by their initial letters. The Sanguine type is high in strength, well balanced and versatile: the Choleric type is also strong, but relatively unbalanced, though versatile: the Phlegmatic type is strong and well balanced but lacks versatility; the Melancholic type is weak, unbalanced, but versatile.

The advantage of displaying these notions in geometrical form is that it reveals at once scope for considerable investigation since four corners of the cube are occupied by question marks. I am going to suggest later that some at least of

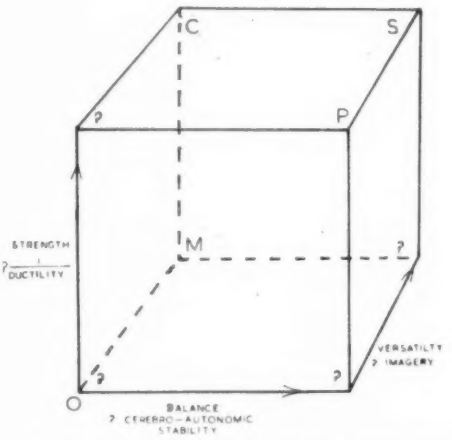

FIG. 1.—Schematic representation of the "Temperament Space" defined by the Pavlovian parameters discussed in the text. The relative positions of the Sanguine, Choleric, Phlegmatic and Melancholic types of temperament are indicated by the initialled dot clusters.

these corners may represent clinical temperaments in the form of neurosis or even psychosis. This proposition has been hinted at in some of the Russian literature, but not as far as I am aware developed very explicitly.

We should now consider more carefully what is meant by these three parameters. The Pavlovian notion of strength we may relate to the span of intensity over which an organism can develop a reasonable response. One might say that it indicates the yield-point under stress. In the simplest test of this variable an animal was subjected to increasing strengths of stimuli, for example, sound, starting as faint buzzes and ending as pistol shots; a strong dog would develop stronger and stronger conditional responses with increasing intensity of stimulation, but a weak dog would start to fail at some intensity and if the response were reversible might actually develop an inhibitory instead of an excitatory response.

I have discussed elsewhere (Walter, 1953) the possible relation of this notion to human character and it is worth considering the possibility that the Pavlovian Strength is related inversely to what we have described as "Ductility" in young people. This in effect is a measure of the extent to which a person is easily led, and is associated in many conditions with an unusual abundance of delta activity in the EEG in posterior brain regions. By our standards, ductility is high in a large proportion of juvenile delinquents and in young people who voluntarily undertake vocations or recreations involving high risks of injury or death. It would be valuable to debate whether this factor may not be related to the scales of introversion and extraversion suggested by Eysenck (1947) and others for purposes of human typology, and also to Cohen's estimate of Subjective Probability (1956).

The parameter called "Balance" by Pavlov was related by him mainly to the equilibrium between cortical inhibition and excitation but these terms have such explicit physiological connotations and central neurophysiology has changed so much that I hesitate to employ them myself in considering psycho-physiological traits which probably involve subcortical systems as well. The phrase that seems to fit our own observations better is something like "cerebro-autonomic stability." This factor we consider related to the interaction between neo-cortical functions, the activities of the limbic structures and the hypothalamic autonomic outflow. Here again perhaps we can see a congruence with Eysenck's parameter of "neuroticism".

The parameter of Versatility—which is found in some Soviet publications under the term "Mobility" or "Adaptability" is of considerable interest in human studies because it may be associated with objectively measurable characters in the EEG. We demonstrated many years ago (Golla *et al.*, 1943) that the responsiveness of human alpha rhythms was related to the mode of habitual imagery, and this suggestion has been developed in detail (Short and Walter, 1954; Walter and Shipton, 1957; Shipton and Walter, 1957; Slatter, 1960). We cannot relate this observation directly to the results of animal experiments since it concerns some sort of symbolic activity in human mentality, but I suspect that even in species with more modest brain development, there may be considerable variation in the manner in which external events are represented in brain activity.

An important feature of the Pavlovian parameters is that in his experience they seemed to be derived from inborn characters, and during the years just before the war there was great interest in typological breeding experiments in Russia. These investigations were interrupted by the war and the subsequent disturbance of scientific freedom, but have been taken up again more recently. Even in laboratory rats, strains of stable and unstable temperament have been recognized for some time and in humans, although breeding experiments are impracticable, studies of identical twins have provided evidence of genetic determination in those factors which can be resolved objectively, such as alpha rhythm characteristics and autonomic reactivity. I understand that in certain of Eysenck's parameters also there is strong evidence of hereditary factors (1956).

When, after the war, we began to apply hypothesis of conditioning to the study of human subjects, I found it helpful to set up for my own benefit a detailed hypothesis of conditioning mechanisms which would allow not only for the obvious and familiar effects of learning by association, but also for the diversity of such mechanisms illustrated by the individual differences such as I have just described. Having little facility for mathematical representation, I presented this theory in terms of seven operational stages. The nature of these operations has been described in detail elsewhere (Walter, 1953), and I need only enumerate the implications and predictions which are relevant to the subject of this paper.

From the physiological standpoint, perhaps the most important inference from this hypothesis is that the nervous system must be provided with

two diffuse projection systems. The first of these should broadcast information about the onset of stimuli in the form of an "on" effect in case such signals are likely to be of importance as *unconditional* stimuli. The second diffuse system should contribute mainly an after-discharge, acting as a widespread short-term storage system in case any particular signal is likely to be significant as a *conditional* stimulus. This prediction was made some years before the existence of such widely projecting "non-specific" systems was actually proved, and in fact it is only quite recently that we have been able to show the reality of these effects in human beings. The second important inference from this hypothesis is that *storage* of information must exist at several grades or levels within the brain. The extension of the neutral (later possibly conditional) signals need not be much more than the after-discharges characteristic of many neuronic networks. The second grade of memory is a more elaborate one, since it involves preservation of degrees of coincidence between specific and conditional brain events. Information of this sort must be preserved over longer periods, though not in permanent form. The third grade of storage might actually be congruent with what we generally call "memory", in the sense that it concerns the impression of significant association, and opens the door to action. It is only at this level of my hypothetical schema that the internal changes produced by conditioning would become apparent in behaviour.

The mechanisms I suggest are in two categories—selection and storage—and the scheme is essentially a statistical one, depending on the acceptance of some criterion of significance quite similar to the criterion of acceptable anti-chance odds that we use in appraising a table of contingency or χ^2. From the purely mechanistic standpoint it is also important that according to this hypothesis a system that starts out newborn, so to speak, with no conditional responses, is in effect making what the statisticians call a "null" hypothesis. It assumes that there are no significant relationships and acts so as to find out whether this assumption is justified. The very young animal acts in play as if anything might happen and its adaptation or conditioning is an indication of what in fact has happened. In a useful, though apparently paradoxical, sense therefore, the process of conditioning is a simplification; of all possible interrelations and associations only a certain selection turn out to be significant, and the system ends under greater constraint than it had at the beginning.

Such a system could seem very extravagant, since it must be prepared to consider many more combinations of events than are likely to be significant. Ashby (1960), realizing this, has suggested that conditioning might be considered as depending not on a detailed *ad hoc* mechanism but on some basic general *tendency* in dynamic systems. What I am proposing is not incompatible with the Ashby theory; the specific hypothetical mechanisms we have been trying to identify and explore in the human brain could well be the product of organic evolution operating on and refining a very general tendency, rather as the general tendency of large molecules to aggregate and duplicate may have been refined into the elaborate mechanisms of genetic reproduction. The higher nervous system does not seem to have evolved toward economy, as neurosurgeons well know, and the spawning of successful mutations depends on extreme genetic prodigality.

In order to illustrate the nature of the experiments now in progress to test this hypothesis at the Burden Institute I will describe some of the results obtained from the study of conditioning three subjects, one normal and two patients under the care of Dr. H. Crow, to whom I am indebted for his permission to study and describe their behaviour under laboratory conditions.

The technique and some of the results of these investigations have been described in other contexts (Cooper *et al.*, 1957; Walter, 1960*a*, *b*). Briefly, the experimental situation may be described as a Type II operant avoidance—defensive conditional reflex (CR). There are two sets of neutral (later potentially conditional) signals. A low-pitched warning tone is combined with a double pattern of stroboscope flashes, or a high-pitched tone with a triplet pattern. The penalty is a painfully loud raucous noise, intense and disagreeable enough to evoke a violent and persistent startle reaction at each presentation. This penalty can be avoided or abbreviated by manual movement of a small lever; for example with the low-doublet combination the lever should be moved to the left, with the high-triplet to the right. The subjects are given no explicit instructions to move the lever but are told that this can stop or avoid the penalty.

The first subject, S.W., is a young electronic engineer with no knowledge of physiology but a wide range of interests. The response charts are drawn with number of trials along the abscissa, success (that is a lever movement which abbreviates or avoids the penalty) is indicated by a cross or circle one scale division up, failure one division down (Fig. 2). Thus a random performance is

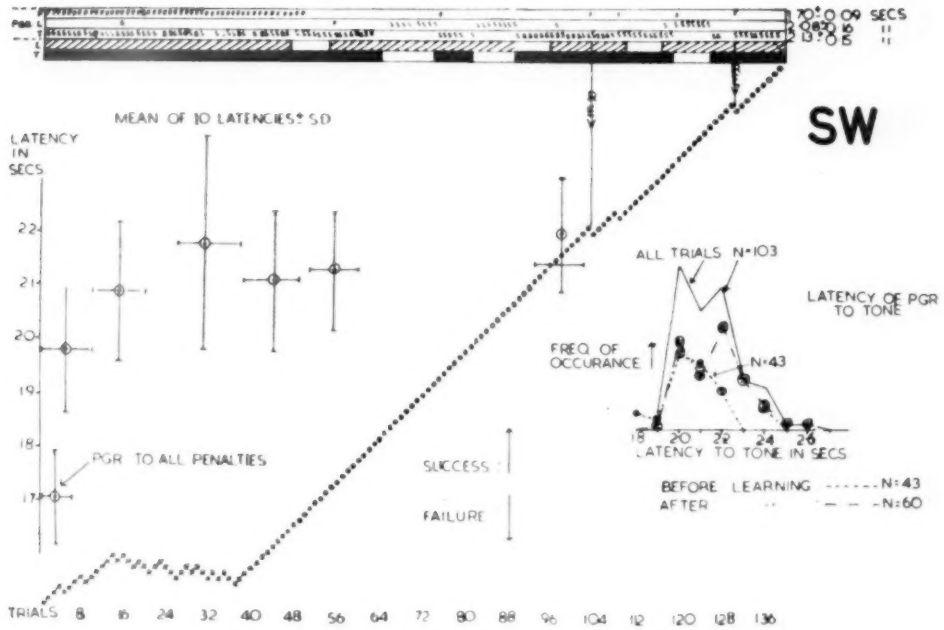

FIG. 2A.—Conditioning curve and PGR latency distributions of subject S.W.

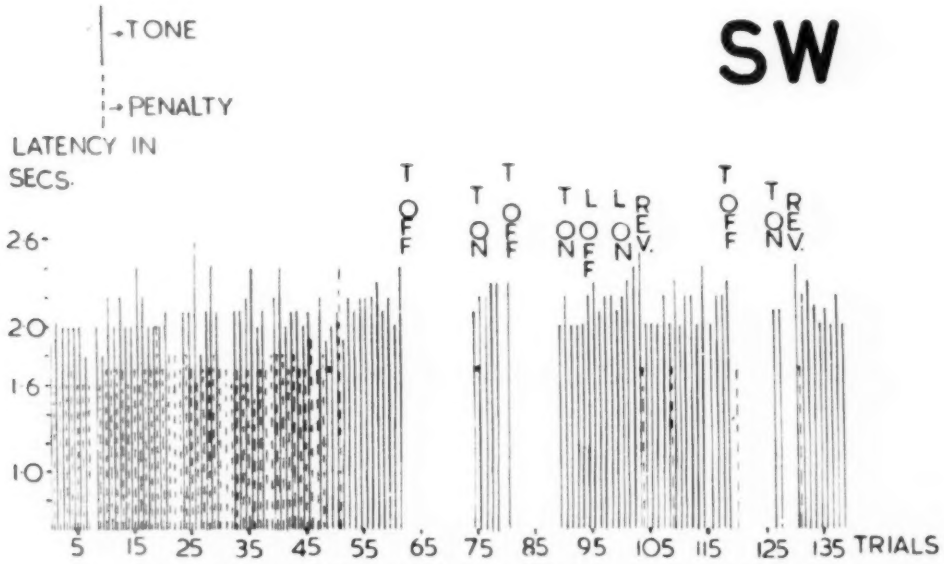

FIG. 2B.— Histogram of PGR latencies during conditioning: responses to UCS are dotted, those to CS solid.

seen as a roughly horizontal curve, perfect performance by one mounting at an angle of 45 degrees. The physiologically unsophisticated subject S.W. began to make correct defensive movements at the 38th trial and correct anticipatory ones at the 49th. The strength and stability of the response were tested by withdrawing and restoring first the visual and then the auditory CS, and by reversing the rules of movement. The CR was, by these standards, firm, balanced and flexible.

The EEG of S.W. shows little rhythmic activity, even at rest with the eyes shut; frequency analysis indicates a small and variable peak at 10–11 c/s in the alpha band, projecting above the background activity only during complete relaxation. This type of record we have called alpha-minus, or M (Golla *et al.*, 1943; Short, 1953; Short and Walter, 1954; Shipton and Walter, 1957). During the conditioning procedure neither the conventional EEG nor the frequency analysis showed any significant change; during the phase of operational success there was an apparent increase in faster activity but reference to the polygraphic tracings shows that this was due merely to augmentation of muscle tone in all parts of the body when the lever was moved. Neither the warning tones nor the rhythmic doublet or triplet flashes seemed to evoke a recognizable response. Even the penalty noise, apart from an occasional movement artifact due to the startle response, had no distinctive effect on the records. On the other hand, careful measurement of the hundred Toposcope exposures does reveal a significant progressive change in the characters of the responses evoked by the visual stimuli. At first these were indistinct and irregular but from about trial 40, when a succession of correct defensive movements started, the evoked responses became sharper and more obviously related to the stimulus pattern. The clarity of the response was *reduced*, however, when the associated warning tone stimulus was withdrawn. This effect continued until the end of the experiment; having once been identified in the Toposcope exposures the development of evoked responses can be distinguished in the primary records, those towards the end showing just above the background, though without the double or triple pattern of the flashes. In this subject therefore the establishment and consolidation of an intentional avoidance CR was associated with enhancement and clarification of the responses evoked by one of the conditional stimuli.

The polygraphic records from this subject reveal further details of the physiological accompaniments of the conditioning. The psychogalvanic responses (PGR) are the clearest indicator; the latency of the responses to the penalty (UCS) averaged $1{\cdot}7 \pm 0{\cdot}09$ sec. while the responses to the tone (CS) averaged $2{\cdot}13 \pm 0{\cdot}15$ sec. The UCS latency was very constant while the CR varied more widely and particularly during the period just before establishment at about trial 35. Statistical analysis of these measurements shows that when classified according to their latencies the responses to the CS fell into two distinct populations, both separate from those to the UCS, and this distinction is particularly clear in those responses occurring after the establishment of the CR. Of the other autonomic variables, only the pulse rate showed a clear relation to the CR formation; between trial 49 and 55, that is when the first series of correct *anticipatory* responses to the CS (tone) appeared, the pulse rate rose from 70 (with marked sinus arrhythmia) to 110/min. There was no change in the blood pressure at this or any other phase.

Even among normal subjects the variation in conditional responsiveness, EEG and autonomic balance is considerable. Several subjects have taken over 150 trials before signs of conditioning appeared and, in general, the clearer and more explicit the prior assumptions by the subject the slower and less stable are the processes of conditioning. In effect, conditionability in this situation depends on lack of prejudice—on starting with a null hypothesis; most subjects expect the signals to follow some sequence or alternation, or to be presented at fixed time intervals. All these factors being deliberately randomized, such expectations hinder adaptation, just as in everyday life a rigid theory or fixed idea may distract attention from the hard facts. The conflict between expectation and actuality often produces marked autonomic disturbance.

This effect is particularly powerful in certain clinical conditions, often ludicrously so. One patient, a plausible pathological liar, made no attempt to perform anticipatory avoidance movements, even when his defensive co-ordination was impeccable. He accounted for this by explaining that he could not expect to know what was wrong unless he was punished!

Although still too elaborate for routine application, the method has proved of interest in cases referred for intensive neuropsychiatric investigation and eventual treatment by intracerebral selective electroleucotomy. One patient,

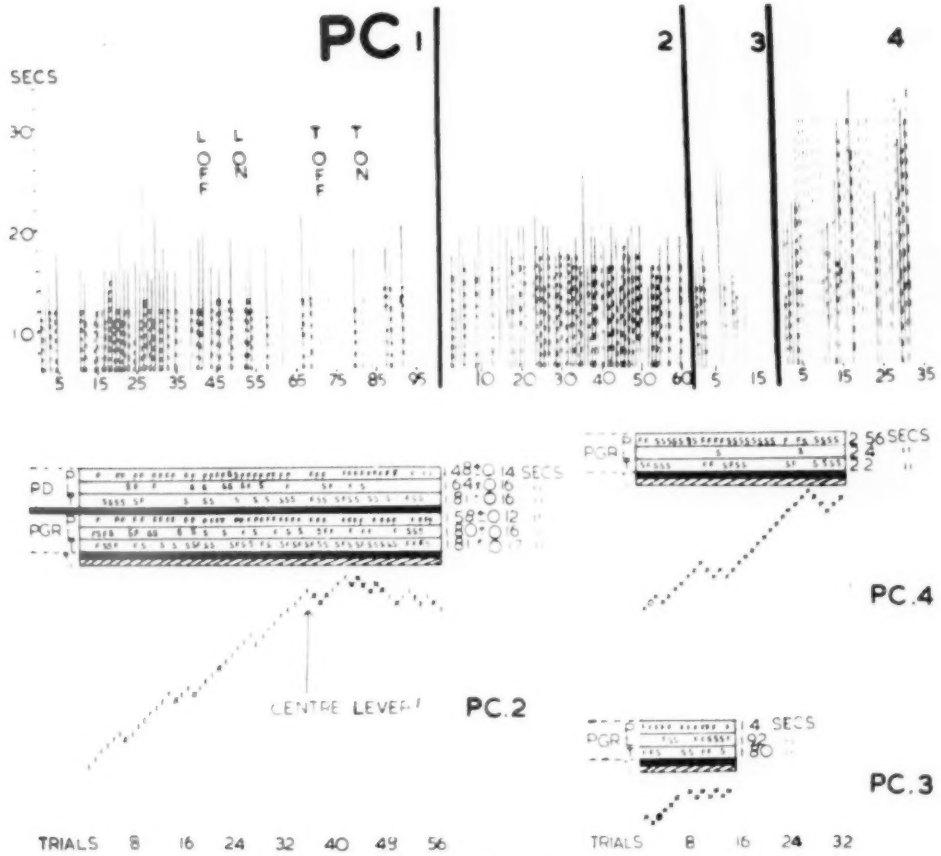

FIG. 3.—Conditioning curves and PGR latencies of patient P. C. before, during and after treatment.

P. C., was a woman of 36 with a twelve-year history of compulsive thinking leading to terrifying delusions with insight. Neither psychotherapy nor physical treatments had been of help. During the conditioning procedure she made no attempt at anticipation or avoidance; instead of centering the lever between trials she held it on one side and moved it to the other when she received the penalty (Fig. 3). She paid no attention to the conditional signals, though they evoked clear autonomic and EEG responses. In fact, all autonomic changes were abnormally brisk; the PGR latencies averaged 1·2 sec for the UCS and 1·7 for the CS instead of 1·7 and 2·1 for normal subjects. When told to centre the lever her responses became entirely random. At this stage intracerebral recordings showed very large and widespread responses in the frontal lobes to auditory and visual stimulation, clear signs of unusual activity of the diffuse non-specific relay systems postulated by the hypothesis outlined above (Fig. 4). These diffuse activating systems are now well defined in animal experiments, but their function has not hitherto been demonstrated within the human nervous system. A notable feature of the non-specific visual responses was their rapid decline with repeated stimulation: the auditory ones persisted indefinitely.

As the treatment of the patient proceeded, involving selective electro-polarization of the frontal white matter, her clinical condition improved and at the same time her autonomic stability as indicated by PGR latencies increased, and the abundance of generalized non-specific cerebral responses dwindled. At this stage she began to make correct discriminatory defensive

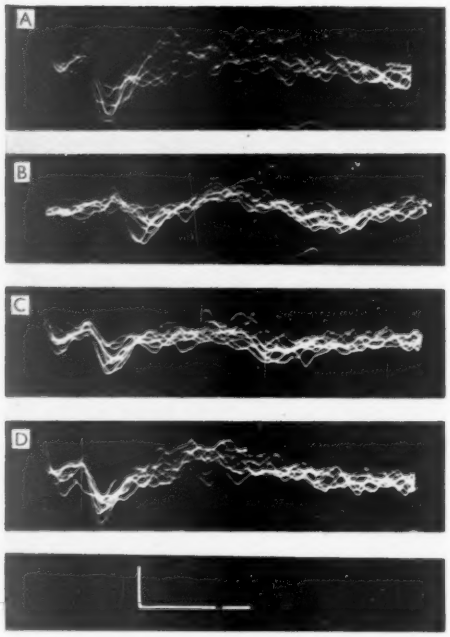

FIG. 4.—Non-specific generalized intracerebral responses deep in frontal lobe to visual and auditory stimuli in patient P. C. A, Responses to 10 clicks at random intervals. B, Responses to random flashes, showing rapid habituation. C, Responses to combined clicks and flashes, attenuated during distraction by conversation. D, Responses to combined stimuli accentuated by attention to stimuli. Calibration: 100 μV, 100 msec.

conditional responses. After the completion of the intracerebral leucotomy, she was able to return home and has remained well. Her PGR latencies are still long but she has never reached the point of anticipatory conditioned movements under laboratory conditions.

Another patient, P. R., was studied and treated in a similar way. She was a woman of 60 with a life-long history of migraine overlaid during the last thirty years by an intractable extension of functional pain leading to suicidal depression. Before treatment her behaviour during conditioning was as ineffective as that of the other patient, but her failure was of a different type (Fig. 5). Nearly all her responses were anticipatory, but they were quite random in direction, and once the lever had been moved to one side it was left there, even when the penalty had been received. Her PGR latencies were long, and at about the 80th trial the conditional responses disappeared, while the latency of the unconditional ones increased to a value greater than that of the conditional latency at the start of the experiment. There were no signs of intracerebral non-specific responses in the frontal lobes, although stereotyped responses persisted in the primary visual pathways and projection cortex.

Like the other patient, P. R. showed no signs of attending to the conditional signals until after intracerebral polarization, when a run of 22 correct anticipatory responses appeared. The conditional reflex was very fragile, however; it was extinguished by omission of the conditional tone, and never fully recovered from this minor disturbance. After further treatment her clinical condition improved enough for her to return home.

These two cases, both showing protracted and intractable disorders of behaviour, illustrate how studies of conditioning may supplement psychiatric examination and diagnostic classification. Reverting to the Pavlovian typology—admittedly too crude for universal application—we can see how such observations as those described above may help to fill out the physiological interpretation of psychiatric disorders. The normal subject, S. W., could be regarded as a "sanguine" type, strong, balanced and versatile; he responded strongly to powerful stimuli, his autonomic activity was in equilibrium with his cortical function even under anomalous conditions and he could respond to either or both of the conditional stimuli. Several normal subjects have shown the characters of the "choleric" type—though strong and versatile they show instability of cortico-autonomic balance; others have seemed "melancholic", others again "phlegmatic" by the same criteria. The positions in the Pavlovian cube that might be assigned to clinical conditions such as those mentioned above is for clinical psychiatrists to decide. There are four empty corners and it is tempting to see in them some reflection at least of the bizarre anomalies observed in our laboratory studies; the first patient, P. C., would not be misrepresented as weak, unstable and stereotyped; but this may be a quite inadequate description of her temperament. The second patient, P. R., may be considered weak and stereotyped but better balanced, but here again we cannot claim that such terms can replace or even usefully supplement the conventional descriptive terminology, though they do suggest experimental as opposed to empirical, approaches to such enigmas.

Two major problems remain to be defined;

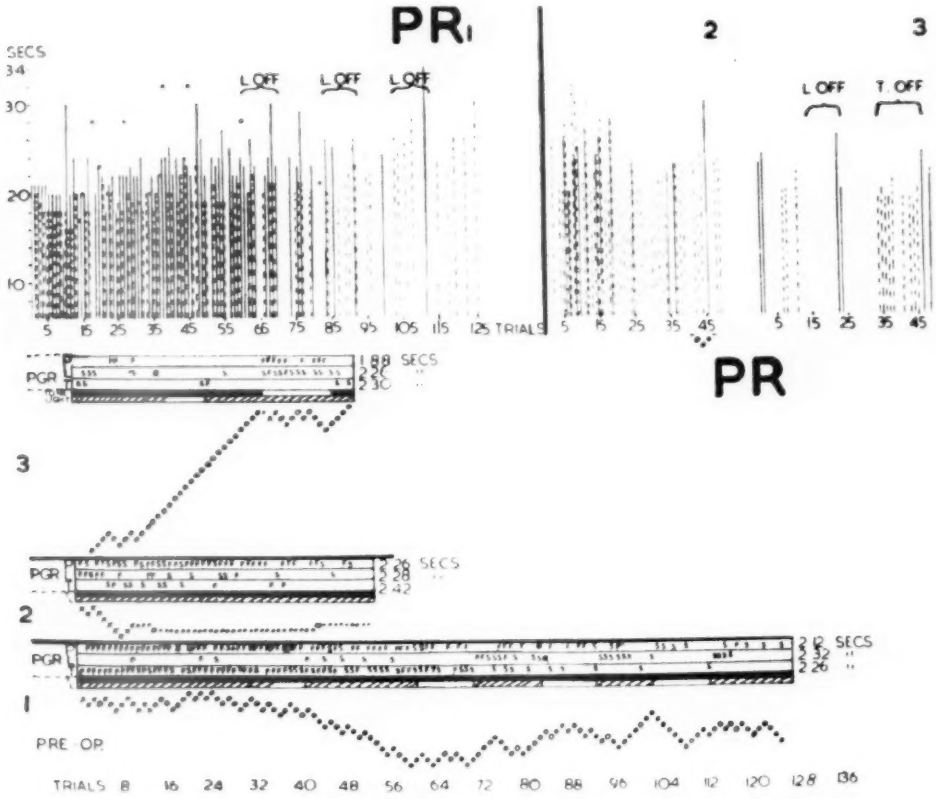

FIG. 5.—Conditioning curves and PGR latencies of patient P. R. before, during and after treatment.

[Figs. 2–5 are reproduced from Walter (1960*a*) by kind permission.]

first the neurophysiological details of the learning mechanisms—are these identifiable in terms of accessible phenomena? For example, are the non-specific generalized electrical responses that vary so much with temperament and situation true indicators of how the brain is working as a significance computer? Second, the temperamental variations which are seen in everyday life as well as clinical practice, and which we have suggested may be formally represented in Fig. 1; are they distributed statistically throughout the whole range of variation, or do they tend to cluster in the extreme positions as the Pavlovian theory suggests? Neither of these problems is easy to define and they can be solved only by long-term combined studies of normal and pathological subjects. The prospect of opening a new approach to mental therapy by such means is the richest reward that physiologists could hope for—but it is not yet within our grasp.

REFERENCES

ASHBY, W. R. (1960) Design for a Brain. 2nd ed. London.

COHEN, J. (1956) Risk and Gambling. London.

COOPER, R., SHIPTON, H. W., SHIPTON, J., WALTER, V. J., and WALTER, W. G. (1957) IV *Int. Congr. Electro-Enceph., Brussels*, p. 339.

EYSENCK, H. J. (1947) The Dimensions of Personality. London.

—— (1956) *Acta psychol., Hague*, **12**, 95.

GOLLA, F. L., HUTTON, E. L., and WALTER, W. G. (1943) *J. ment. Sci.*, **89**, 216.

SHIPTON, J., and WALTER, W. G. (1957) In: Conditionnement et Réactivité en E.E.G. Edited by H. Fischgold and H. Castaut. Paris; p. 185.

SHORT, P. L. (1953) *Brit. J. Psychol.*, **44**, 38.

——, and WALTER, W. G. (1954) *Electroenceph. clin. Neurophysiol.*, **6**, 29.

SLATTER, K. H. (1960) *Electroenceph. clin. Neurophysiol.* (in press).

WALTER, W. G. (1953) The Living Brain. London.

—— (1960*a*) *Amer. J. Psychiat.*, **116**, 673.

—— (1960*b*) Moscow Colloquium on Higher Nervous Activity and E.E.G. Montreal. (In press.)

——, and SHIPTON, J. (1957) In: Conditionnement et Réactivité en E.E.G. Edited by H. Fischgold and H. Castaut. Paris; p. 177.

Personality and Behaviour Therapy

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Introduction

Most psychiatrists will probably agree that the diagnosis and therapy of neurotic disorders is not as advanced as one might have hoped after so many years of research and application. In 1952 I reviewed the evidence for the effectiveness of psychotherapy with adults; the conclusion was that the data published to date failed to show any beneficial effects of psychotherapy. Levitt in 1957 carried out a similar review for work with children, and came to a similar conclusion. These findings are in full agreement with the pessimism with which Freud in his later years regarded the therapeutic possibilities of his own techniques. Dr. H. T. Weinstock, the chairman of the fact-finding committee of the American Psychoanalytical Society, has recently stated that "no claims regarding the therapeutic usefulness of neurotic treatment are made by the American Psychoanalytical Society", and in this country Glover (1955) has explicitly disavowed any claims for therapeutic usefulness of psychoanalytical methods. Schmideberg (1958) can be quoted in a similar vein, and several psychotherapists like J. Wolpe (1958) and A. Ellis (1955, 1957) have become so disillusioned with the effects of psychoanalytical therapy that they have turned to other methods which on comparison were considerably more successful.

On looking for better methods we may with advantage consider the usual way in which science helps in the solution of practical problems. Pure research builds up a systematic scheme uniting established *facts*, *laws* expressing in a quantitative manner the relations between these facts, and general *theories* explaining these facts in terms of a general framework from which deductions can be made in relation to situations not hitherto studied. Considered in this way, it is clear that psychotherapy and psychoanalysis have not followed this method at all. So far from deducing methods of treatment from experimentally established facts and laws of general behaviour, Freud tried to reverse the process and to deduce these general facts and laws from the process of psychotherapy itself.

Freud had some justification for his procedure because academic psychology offered him little that would have been helpful in his task. Modern psychiatry is more favourably placed because it has available a great wealth of fact and theory relating to the acquisition of neurotic responses and symptoms. I am referring to modern learning theory, built up by Hull, Spence, Mowrer, Miller and many others on the firm foundation of Pavlov's original work. If we agree that neurotic symptoms are *learned* responses rather than being innate or due to lesions of one kind or another, then it seems to me to follow almost without argument that if we are to look for an answer to the problems of the causes and cures of neurosis, we must turn to modern learning theory and attempt to apply its laws to the problems of psychiatric practice. Such a procedure holds the exciting promise that it may result in a *rational* system of diagnosis, treatment and prophylaxis, to take the place of the purely *notional* or at best *empirical* procedures now found (Eysenck, 1959).

The Causes of Neurosis

In attempting to carry through such an application of modern learning theory to neurosis I would like to begin by postulating that neurotic symptoms are *learned patterns of behaviour* which for some reason or another are *unadaptive*. The paradigm of neurotic symptom formation would be Watson's famous experiment in which, by a simple process of classic Pavlovian conditioning, Watson and Raynor (1920) caused a phobia for white rats in an 11-months-old boy ("little Albert") by standing behind him and making a very loud noise whenever the infant reached for the animal. The animal was the *conditioned stimulus* in the experiment, the loud fear-producing noise was the *unconditioned stimulus*, and the sympathetic fear response, as predicted, became conditioned to the CS (the rat). In this way a phobia for rats and indeed for all furry animals was experimentally set up.

If we can extrapolate from this laboratory experiment to live situations, we would postulate that maladaptive conditioned fear responses can arise either from single traumatic events, i.e. events causing extremely strong sympathetic reactions, or from the repetition of subtraumatic stimuli causing somewhat weaker sympathetic

reactions. As an example, consider the case of the patient who complained that he was always impotent when attempting to have intercourse with his wife at home; he did not experience any impotence elsewhere. It appeared that as a young man this patient had been surprised by an irate husband in the process of seducing his wife; the husband thrashed the patient within an inch of his life, i.e. he produced a very traumatic sympathetic response. According to learning theory any accidental stimulus which attracted the attention of the patient in the period of a second or so before the onset of the unconditioned stimulus would acquire the properties of a conditioned stimulus producing a sympathetic reaction. The choice of conditioned stimulus under these circumstances is purely fortuitous; as it happened the patient's gaze rested on the wallpaper of the room in which he received his punishment. By an unlikely coincidence the wallpaper of the bedroom in his home had exactly the same pattern on it. The sequence now becomes clear. The conditioned stimulus situation: amorous disposition plus sight of wallpaper, produces the conditioned response, i.e. sympathetic arousal; this inhibits the parasympathetic arousal necessary to produce erection. It is clear now why no impotence was felt elsewhere, and as a final proof of the hypothesis a change in wallpaper produced the immediate cessation of the symptoms.

Anyone reading through the thousands of histories in the literature from this point of view will be surprised to discover in how many cases a simple conditioning paradigm will fit the facts much better than the complex, circuitous and improbable explanation given by analytically trained observers. Wolpe and Rachman (1961) have recently re-analysed Freud's case of "little Hans" in this manner, and it is extremely instructive to see how easily all the pieces fall into place once we accept the conditioning paradigm.

The Persistence of Neurosis

Granted that neurotic symptoms are *created* through a process of conditioning we may yet wonder why they do not *extinguish* rather quickly when no reinforcement is forthcoming. It is well known that conditioned responses extinguish readily when not reinforced; why are neurotic symptoms an exception to this rule? The answer to this problem comes in several parts. In the first place, it is almost certain that many conditioned autonomic responses do in fact extinguish relatively quickly; it is those which do not so extinguish which cause the patient to complain and which therefore come under observation.

In the second place, it should be noted that conditioned responses extinguish only when the conditioned stimulus is presented repeatedly without the presentation of the unconditioned stimulus. Now consider the case of the typical neurotic phobia, say that of little Albert's fear of white rats. If he were a Pavlovian dog, strapped in his stand in the laboratory, we might be able to present him with series of white rats and extinguish conditioned response by failing to provide the unconditioned stimulus, i.e. the loud noise. But little Albert is a free agent, and given his conditioned fear of white rats he will *avoid* any contact with them, thus making impossible the extinction process by making it impossible to associate the conditioned stimulus with the absence of the unconditioned stimulus; in other words he will refuse to do what is sometimes called "reality testing".

In the third place there is a further mechanism to be considered. If little Albert sees a white rat he will have a strong and unpleasant sympathetic reaction. He quickly withdraws from the situation, and this withdrawal is followed by reinforcement in the form of a lessening of the conditioned sympathetic fear response. Thus through a process of secondary reinforcement little Albert will build up a strong avoidance reaction, leading him away from the conditioned stimulus, thus making it even more difficult for a process of extinction to occur. We thus have a vicious circle which protects the conditioned fear response from extinction.[1]

Personality and Neurosis

The argument so far presented is quite general, applying to everyone indiscriminately. It is well known, however, that people differ profoundly with respect to their conditionability, i.e. the *speed* with which conditioned responses are formed, the *strength* of these conditioned responses and their *resistance* to *extinction*. Similarly it is well known that people differ profoundly with respect to their *autonomic lability*, i.e. the *speed of reaction* of the autonomic system, the *strength of reaction* of the autonomic system, and the speed with which the autonomic system *returns to its original level*. I have argued elsewhere that these two great classes of phenomena are related closely to two major dimensions of personality (Eysenck, 1957). It appears that speed of conditioning, strength of conditioning and slowness in extinction are characteristic of *introverted people*, while poor conditionability in

[1]There is no space here to treat of another consideration, viz. Solomon and Wynne's (1954) principle of "anxiety conservation and partial irreversibility."

all aspects is characteristic of *extroverts*. If we take the personality dimension of *neuroticism*, we would argue that towards the neurotic end we have *strong* reaction and long *persistence* of autonomic reactions, while towards the normal end we have a weaker arousal and a stronger damping effect. It would seem that a conjunction of introversion and neuroticism would be most likely to result in all sorts of conditioned anxiety and fear reactions, phobias, &c., and indeed the evidence is strongly in favour of such a deduction. People in what I have called the dysthymic group, i.e. those high on neuroticism and on introversion, have indeed been found to be exceedingly quick in the formation of conditioned responses, and it is significant that individuals in this group make up three-quarters or more of psychiatric patients who are diagnosed as neurotics. These personality characteristics of autonomic lability and quick or slow conditionability are assumed to be *constitutional* features of the individual, but they can of course also be manipulated experimentally. Central nervous system depressant drugs have an extrovertory effect and decrease conditioning, while stimulant drugs have an introvertory effect and facilitate conditioning. Similarly, barbiturates *decrease* autonomic lability while adrenaline *increases* it. Other environmental features also have effects on these dimensions; thus for instance brain damage and old age would appear to reduce the speed and effectiveness of conditioning.

The Cures of Neurosis

In this section I shall concentrate on dysthymic disorders, i.e. conditioned fear and anxiety reactions of one kind or another. We have seen how these responses are acquired through a process of conditioning, and how they are resistant to the process of extinction. The task of learning theory is to suggest to us methods for breaking down this resistance to extinction, and for reducing the conditioned maladaptive responses to subthreshold level. Many such methods are in fact available, and I can only touch lightly on some of them. The first and most obvious one, but also probably the least useful, is *physical manipulation* of the environment. Thus removal of the wallpaper in the case quoted above completely cured the impotence. Unfortunately, it is rare for such obvious solutions to present themselves.

Equally obvious, but rather more useful, is *aversion therapy*, i.e. the conjunction of symptom and some form of punishment. I refer to the well-known work of Liversedge and Sylvester (1955), Sylvester and Liversedge (1960) and Beech (1960) on writer's cramp, in which they have shown that the administration of electric shock whenever the cramplike movements complained of occurred served to extinguish the latter. Similar is the procedure used by Freund (1958) to cure homosexuality by associating stimulation produced by photographs of nude males with drugs producing vomiting. A similar technique was recently used by Raymond (1956) in a case of fetishism. Alcoholism has frequently been treated in this fashion.

Positive conditioning is another method of great fruitfulness; the classic example of its application is probably enuresis. Gwynne-Jones (1960) has made an impressive analysis of the literature. Conditioning treatment appears to be decisively superior to any other method hitherto tried.

Much more unusual than the preceding methods is that of *conditioned inhibition* or "negative practice". According to this theory massed practice of any activity sets up a fatigue-like state of inhibition which dissipates during subsequent rest periods. Such dissipation acts as a reinforcement for the prevailing state which is one of *not* carrying out the activity in question; this prevailing state, being reinforced, becomes conditioned to the stimuli available at the time, and we obtain conditioned inhibition i.e. a habit of *not* reacting in the manner practised to the stimuli which were present during the practice period. An excellent example is Yates and Gwynne-Jones' work (Eysenck, 1960) on tics; they demonstrated that by causing patients voluntarily to practise their tics as quickly and as strongly as possible, they succeed in diminishing and in some cases completely extinguishing the tic. Here is a method which would appear to have great possibilities for the future.

Last among the methods briefly reviewed, but first from the point of view of general importance, I would place that of *reciprocal inhibition*, as described by Wolpe (1958). In this method the essential feature is the elaboration of a conditioned response antagonistic to the symptom which is to be abolished. The difficulty here, as we have seen before, is the impossibility of causing patients to undergo "reality testing". Wolpe has shown how to make use of the concept of "stimulus gradients" in this connexion. Such gradients can be of many kinds. Thus, little Albert, when fully grown, may have a fear of rats which amounts to ten points on an arbitrary scale. His fear of rats as shown in a film might only be seven points. His fear of rats shown in a

drawing might only be three points. His fear of hearing the word "rats" spoken might only be two points, and his fear of imagining a rat way off in the distance might only be one point. Somewhere on this continuum the therapist can find a reaction weak enough to start breaking into the vicious circle so that he can build up a positive conditioned response which will generalize to those levels hitherto inaccessible. In the case of little Albert such a gradient might be created by simply increasing the distance of the rat from the child (Jones, 1924); with the rat in the other corner of the room the infant was in fact not much worried and would accept a piece of chocolate. By gradually bringing the rat nearer and nearer, and each time giving him a piece of chocolate, it was found possible finally to extinguish the phobia completely. Wolpe (1958) in his experimentally ingenious and theoretically important series of experiments has shown that this principle can be applied to many types of severe adult neurosis with similar effects. His book discusses the methods used in great detail; it ought to be required reading for every budding psychiatrist.

The Value of Symptomatic Treatment

Throughout this paper I have stressed entirely the treatment of *symptoms* without alluding to any underlying *complex* or illness. The reason is that *as far as learning theory is concerned there is no illness and there is no complex*. We are dealing entirely and exclusively with maladaptive habits formed through a process of conditioning, and capable of being extinguished through one of the several methods outlined above. It is this stress on the symptom and its abolition which distinguishes behaviour therapy most decisively from psychotherapy with its stress on hypothetical underlying complexes and disease processes (Yates, 1958). The analytic psychotherapist might reasonably ask two questions. In the first instance he might wonder just how successful behaviour therapy was in getting rid of symptoms, and in the second place he might wonder whether there was not likely to be a recrudescence of symptoms even after apparently successful therapy.

The answer to the first question is not known. What is obviously required is a properly controlled experimental comparison, with cases assigned at random, in which one group was treated by means of behaviour therapy, and another by means of psychotherapy. No such experiment has yet been done, and only comparisons of published data are possible. The difficulties and pitfalls involved in such comparisons are well known; I shall here give only my own impression of what the data suggest to me. In the first place, then, it seems that behaviour therapy is most successful when it deals with monosymptomatic disorders such as enuresis, writer's cramp, tics, phobias, &c. For these disorders it is possible to assess very accurately the success or failure of the treatment in quantitative form, and it seems likely to me that the accuracy of the criterion is responsible for the marked *demonstrable* superiority in success of treatment. In the second place, however, it should by no means be assumed that the more usual and less clear-cut psychiatric disorders cannot be treated with considerable success as well. Wolpe (1958) has shown that in a group of over 120 cases the rate of success of treatment was considerably greater, and the time taken was much less, than in typical psychoanalytical treatment. The highly significant differences he has published cry out for a proper experiment to be set up in which these claims could be impartially evaluated.

In the third place it does not seem as if the fears of the analysts were justified in so far as recrudescence of symptoms is concerned. A survey of the literature has shown that even those behaviour therapists whose analytic background made them particularly sensitive to this problem, entirely failed to discover the expected return of the symptom. Indeed the facts point in the opposite direction. Once a major symptom has been extinguished, there is an all-round improvement with respect to other symptoms, a lessening of anxiety, an improvement in social, sexual and work relations, and quite generally a transfer from a *vicious* circle to a *beneficial* one. Here also of course the literature is by no means sufficient to come to a definite conclusion (Yates, 1958). However, the findings are striking enough to make one doubt very much the universal validity of the Freudian argument, and to demand more proof than has ever been given so far of the validity of this belief. The evidence I have been able to see certainly supports the contrary interpretation.

Summary and Conclusions

In this brief paper I have outlined the basic tenets of behaviour therapy, its relation to personality study and the deductions made from learning theory to the treatment of neurosis. I have tried to show in what way learning theory can help in suggesting new types of treatment, and I have tried to indicate the relative success or failure of these treatments when compared with analytic psychotherapy. The general conclusion I think

must be that here we have a method of treatment which is rational, deduced from an existing body of information along rigorous lines, and also responsible for a large number of successful applications. It will be clear that this method is a genuine alternative to psychotherapy as usually practised, and it will also be clear that in my view it is a superior method. Time seems to be ripe for experimental and clinical trials to be held in an attempt to assess the relative merits of these two methods.

REFERENCES

Beech, R. (1960) In: Behaviour Therapy and the Neuroses. Ed., H. J. Eysenck. London; p. 349.

Ellis, A. (1955) *J. clin. Psychol.*, **11,** 208.

—— (1957) *J. clin. Psychol.*, **13,** 344.

Eysenck, H. J. (1952) *J. consult. Psychol.*, **16,** 319.

—— (1957) The Dynamics of Anxiety and Hysteria. London.

—— (1959) *J. ment. Sci.*, **105,** 61.

——, Ed. (1960) Behaviour Therapy and the Neuroses. London.

Freund, K. (1958) *Acta neuropsich. argentina*, **4,** 233.

Glover, E. (1955) The Technique of Psychoanalysis. London.

Gwynne-Jones, H. (1960) In: Behaviour Therapy and the Neuroses. Ed. H. J. Eysenck. London; p. 250.

Jones, M. C. (1924) *J. exp. Psychol.*, **7,** 383.

Levitt, G. E. (1957) *J. consult. Psychol.*, **21,** 189.

Liversedge, L. A., and Sylvester, J. D. (1955) *Lancet*, i, 1147.

Raymond, M. J. (1956) *Brit. med. J.*, ii, 854.

Schmideberg, M. (1958) *Psychoanal. Quart.*, **27,** 1.

Solomon, R. L., and Wynne, L. C. (1954) *Psychol. Rev.*, **61,** 353.

Sylvester, J. D., and Liversedge, L. A. (1960) In: Behaviour Therapy and the Neuroses. Ed. H. J. Eysenck. London; p. 334.

Watson, J. B., and Raynor, R. (1920) *J. exp. Psychol.*, **3,** 1.

Wolpe, J. (1958) Psychotherapy by Reciprocal Inhibition. Stanford.

——, and Rachman, S. (1961) *J. nerv. ment. Dis.* (to be published).

Yates, A. J. (1958) *Psychol. Rev.*, **65,** 371.

—— (1960) In: Behaviour Therapy and the Neuroses. Ed., H. J. Eysenck. London; p. 236.

The following paper was also read:

Cybernetic Aspects of Conditioning and Treatment.—Dr. W. Ross Ashby (Bristol).

Meeting
March 8, 1960

The following papers were read:

The Bereavement Factor in Depressive Illness.—Dr. Felix Brown. To be published in full in the *J. ment. Sci.*

Grief and Mourning in Infancy.—Dr. John Bowlby. To be published in the *Psychoanal. Study Child*, 1960, **15.**

Meeting
April 12, 1960

A discussion was held on **Enuresis.**

The opening speakers were Dr. Emanuel Miller, Dr. Samuel Dimson and Dr. H. Gwynne-Jones.

The paper by Dr. H. Gwynne-Jones forms the basis of a chapter in the book: Behaviour Therapy and the Neuroses, edited by H. J. Eysenck, 1960. London; p. 377.

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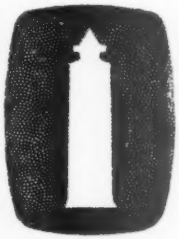

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Meeting
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Obstetric Analgesia Based on Pethidine-Antagonist Mixtures [*Abridged*]

By John Bullough, M.B., F.F.A. R.C.S.
Dartford

In this country the great majority of labours are conducted by midwives. Any method of relieving pain in childbirth, to be of real value, must be suitable for their use. I will confine myself to such methods.

The work described here was carried out at the Maternity Unit, West Hill Hospital, Dartford, Kent, with 53 beds. 1,500 mothers are delivered annually; 92% of these are booked cases; 64% are primigravidæ; while 55% are abnormal in some way.

Until 1954 analgesia was based on the inhalation of gas-air from Minnitt's apparatus. Chloral was the routine sedative in early labour; pethidine in 100 mg doses in late first stage. 80% of all cases received 100 or 200 mg of pethidine, which is the maximum allowed for use by midwives without special permission.

The disadvantage of pethidine is that with this dosage only half the mothers experience good analgesia. If higher doses are used there is an increasing risk to the baby, as the drug crosses the placenta and causes depression of respiratory reflexes at birth.

With the introduction of the specific opiate antagonist nalorphine (n-allylnormorphine, Lethidrone) pethidine-induced respiratory depression need no longer be feared. This drug can prevent or correct respiratory depression due to morphine, pethidine, or other opiates, (but not that due to other drugs). In obstetrics the drug may be given to the mother a sufficient time before delivery to allow transmission to the baby (Eckenhoff *et al.*, 1953); or it can be given to the baby if he fails to breathe in a reasonable time after birth (Eckenhoff *et al.*, 1953; Paterson and Prescott, 1954). Both methods give good results, but are unsuitable for routine use by midwives.

In 1952, when I first used nalorphine, a third possible way of using the drug occurred to me, namely, to mix it with pethidine, before injection, in an amount sufficient to neutralize the respiratory depressant action of the latter. I hoped to find a drug mixture which would produce analgesia without respiratory depression. Such a preparation would be unique.

Clinical Studies

I carried out studies for two years before such a mixture was used in obstetrics. Respiratory measurements in lightly anæsthetized subjects were made with (1) spirometric tracings (Bullough, 1958, 1959*a*) and (2) minute-respiratory-volume charting, using a non-rebreathing technique (Bullough, 1955), or a ventilation meter and stopwatch. Continuous analysis of end-tidal gases for carbon dioxide concentration (Nunn and Pincock, 1957) was done later.

To find the least amount of antagonist which neutralized the respiratory depression caused by pethidine or similar drug the following techniques were used: (1) A dose of pethidine was given to produce respiratory depression, then fractional doses of antagonist were given until respiration returned to the control level. (2) A dose of antagonist was given, followed by fractional doses of pethidine until respiratory depression appeared. (3) Mixtures of the two drugs, based on the results of the two previous methods, were used by intramuscular or continuous intravenous injection, or both, and any respiratory effects noted. Analgesic and narcotic activity were also recorded.

There are a number of difficulties in the interpretation of such studies (Bullough, 1959*a*) but the main conclusions are clear.

Results of Clinical Studies

Pethidine in analgesic doses always depresses respiration, primarily by slowing the rate. 100 mg intramuscularly starts to act in four minutes, respiratory depression is at its maximum after fourteen minutes, and some effect is still present forty-five minutes later. Repeated doses have a cumulative effect on respiration; this is one of the main disadvantages of the drug. The depression from 100 mg pethidine is prevented by the previous administration of 5 mg nalorphine; or corrected by this dosage if given afterwards, but the antagonist is more effective if given first.

Rapid intravenous injection of a mixture of pethidine 100 mg and nalorphine 5 mg causes a short depression lasting three to six minutes.

Pethidine acts first, and is quickly neutralized. This dose of pethidine alone would almost invariably cause respiratory arrest for some time during anæsthesia. Intramuscular injection of this mixture causes sedation and analgesia without detectable respiratory depression on single or repeated doses. This mixture was extensively used as premedication, as a supplement to nitrous oxide anæsthesia, and to relieve various types of pain. Provided this amount of antagonist is not exceeded there is little, if any, observable loss of analgesic effect.

A patient who has received the mixture differs from one who has received pethidine alone in that there is more drowsiness, less euphoria, the face is less pink and may be pale, the peripheral veins are less dilated, the pupils are less constricted, respiration and cough reflexes are not depressed.

In 1954 I suggested that the pethidine-nalorphine mixture should be used in obstetrics. With the full co-operation of the medical and maternity staff—to whom my thanks are due—trials were started. For four months half the patients received the mixture, the remainder pethidine alone. The results in 375 cases were collected by my registrar and published (Baker, 1957). The mixture was found to be superior to pethidine in all respects both for mothers and babies.

For two and a half years thereafter all patients received the mixture (2,500 cases). Comprehensive clinical data were recorded on specially prepared forms (42 items) by two specially appointed senior midwives. They obtained information from case-sheets, midwives conducting the labours, and from the patients at interview the day after delivery.

The data from 1,300 consecutive patients receiving the mixture and from 265 patients receiving no pethidine were subjected to statistical analysis to determine whether the mixture affected the baby. It was concluded that there was no significant effect on the baby in normal or abnormal cases, irrespective of whether the pethidine mixture had been given in low or high dosage. In contrast to these findings pethidine can be shown to affect the baby, especially when given in high dosage to the mother (Paterson and Prescott, 1954; Roberts *et al.*, 1957).

The midwives were encouraged to use the mixture freely to promote good analgesia and sedation; the average dose of pethidine per patient rose from 170 to 218 mg. This was partly due to its more common use in patients in whom some difficulty was expected, as it was later found that in the early cases pethidine had often been withheld for fear of the effect on the baby (*see* Table I: the "pethidine only" series has a low proportion of abnormal cases and a low incidence of operative interference; there is a high figure for the latter in the "no pethidine" series).

Levallorphan.—In 1957 a second antagonist became available, levallorphan (Lorfan). This drug bears the same relationship to the analgesic levorphan (Dromoran) as nalorphine bears to morphine. I investigated and used the drug clinically in the same way as nalorphine.

The main difference between the two antagonists is as follows: levallorphan is a more potent respiratory antagonist, so that less is required (approximately 1·25 – 1·5 mg to neutralize 100 mg pethidine); in this dosage it causes less drowsiness than nalorphine, has no analgesic action of its own (as nalorphine has) and is longer-acting.

In the first instance I used, for obstetrics, a mixture containing pethidine 100 mg and levallorphan 2·0 mg—a ratio of 50/1. Although this mixture contains an excess of antagonist the results in 129 consecutive cases were very satisfactory, especially as regards the babies (Bullough, 1959*b*). The average dose of pethidine in this series was 240 mg.

I was later invited to conduct trials with a mixture containing pethidine 100 mg and levallorphan 1·25 mg—a ratio of 80/1 (Pethilorfan). This preparation has been in continuous use since 1958. It has been used in 2,500 obstetric patients (involving 12,000 injections), and is in routine use as premedication, as a supplement to nitrous oxide anæsthesia, and for the relief of pain when respiratory depression is to be avoided.

Obstetric Analgesia: Results

The following series of cases were compared on the usual criteria (Sturrock, 1939). Pethidine-nalorphine (5 mg) mixture, 1,030 cases; pethidine-levallorphan (1·25 mg) mixture, 700 cases; pethidine alone, 297 cases; no pethidine used, 283 cases. The last were mostly patients coming into hospital late in labour, i.e. too late for an injection of analgesic to be given. In each series the dose of pethidine was always 100 mg per injection (Table I).

In selected primigravidæ with reasonably normal labours, the mean dose per patient has only risen in the most recent series, largely as a result of the drug being given earlier in labour, since the dosage per hour has not changed. Maternal analgesia, amnesia and co-operation were better in the antagonist series, usually significantly so by statistical tests. This is because a good effect from the injections leads to better results from gas-air inhalation, and to better co-operation, provided the patient is not

TABLE I

	Pethidine + nalorphine	Pethidine + levall-orphan	Pethidine alone	No pethidine
No. of cases in series	1,030	700	297	283
EFFECTS ON MOTHER				
(Selected primigravidæ, see Appendix A)				
Good results from injections, %				
according to mother	84§	74‡	57	
according to midwife	83*	88*	87	
Good results from gas-air, %				
according to mother	84§	75†	51	
according to midwife	84†	82†	62	
Good amnesia, incidence %	54†	51†	30	
Good co-operation, incidence %	88‡	80*	64	
Mean total dosage; mg	210	231	210	
DOSAGE-TIME RATIO ALL CASES				
Mean total dose pethidine mg	218	257	172	
Mean time from first injection to delivery, hours	7·1	9·5	5·8	
Mean time from last injection to delivery, hours	3·3	3·4	2·9	
Mean time from first to last injection, hours	4·8	6·1	2·9	
Mean dosage, mg hour	30	27	29	
EFFECTS ON UTERUS				
(Selected primigravidæ, see Appendix A)				
Mean duration first stage, hours	12·7	12·5	12·7	7·2
First stage over 24 hours, %	12*	12*	10	1·9
Mean duration second stage, minutes	60	62	57	46
Second stage over 2 hours, %	9·6*	8·7*	4·1	2
Third stage over 20 minutes, %	5·9	2·9	14·7	3·8
Operative deliveries, % (not comparable statistically)	8·2	9·0	4·4	13·2
Fœtal mortality, % (not comparable)	1·4	1·2	1·0	3·6
(forceps deliveries; *see* Fig. 1)				
Post-partum hæmorrhage, % all cases	1·5*	1·7*	0·3	1·3*
Manual removal of placenta, % all cases	1·8*	2·0*	2·0	1·0*
EFFECTS ON BABY				
(Classification, see Appendix B)				
All cases: incidence Class I babies, %	74†	76†	67	78†
All cases: incidence Class III babies, %	3·6	5·4	5·7	1·8†
"Normal" cases only, see Appendix C				
Low dose: Class I babies, %	86§	89§	71	91§
Low dose: Class III babies, %	0·7	0·5	2·8	0·8
High dose: Class I babies, %	84	77	81	
High dose: Class III babies, %	0	2	9·5	
"Abnormal" cases only				
High dose: Class III babies, %	11	10	15	2·6
Proportion of "abnormal" cases in series, %	55	55	45	55
EFFECTS OF TIME AND PLACENTAL TRANSMISSION				
Time from last injection to birth, all cases:				
under 3 hours Class I babies, %	78	81	74	
over 3 hours Class I babies, %	70	68	57	
under 3 hours Class III babies, %	2	3·4	4·4	
over 3 hours Class III babies, %	5·8	8·2	8·2	

Results of statistical analysis where there are sufficient cases to be compared are given as follows on χ^2 test:

* Not significantly different from pethidine series.
† Significantly better than pethidine series; P = 0·05–0·02.
‡ Very significantly better; P = 0·01.
§ Very highly significantly better; P = 0·001.

APPENDIX A.—SELECTED PRIMIGRAVIDÆ

(For studies of effects on mother and uterus)

Age 15–35 years.
No ante-natal complication except toxæmia.
Gestation, 37 weeks and over.
Commenced labour normally (i.e. A.R.M. excluded).
No other drugs except chloral, pethidine, antagonists, gas-air, trilene-air.
No general anæsthetic.
Spontaneous vertex anterior delivery only.

APPENDIX B.—CLASSIFICATION OF BABY'S CONDITION AT BIRTH

CLASS I (Definitely unaffected). Breathed or cried within one minute of birth; no treatment other than wiping of nose and mouth with swab.

CLASS II (Slightly or moderately depressed). Either did not breathe within one minute, or was given nasal oxygen, or required pharyngeal suction. (Most failed to breathe in one minute; half received oxygen.)

CLASS III (Definitely depressed, shocked or asphyxiated). Did not breathe or cry within five minutes of birth and required pharyngeal suction and oxygen.

APPENDIX B, *contd.*

CLASS IV Depressed at birth; died within forty-eight hours.

CLASS V Stillborn.

For comparison of drug action the clearest picture is obtained by studying Class I and Class III babies. Fœtal deaths are almost invariably associated with some definite obstetric, fœtal or placental abnormality, and proved of no value for comparison in these series; the majority occurred in the series receiving no pethidine.

APPENDIX C.—SELECTION OF "NORMAL" CASES

(For study of baby's condition at birth)

NORMAL: "Booked."
No ante-natal complications.
No other drugs except chloral, pethidine, antagonists, gas-air, trilene-air.
No general anæsthetic.
Cord not tight round neck at birth.

ABNORMAL: Remaining cases.

Low dose = 100–200 mg. high dose = 300 mg and over.

over-sedated. Improved amnesia is probably attributable to the weak narcotic effect of the antagonists, especially nalorphine, as pethidine itself has almost negligible amnesic effects (Barnes, 1947).

There is no significant difference in the effects on the uterus. There is, however, a suggestion that pethidine can accelerate the second stage and delay the third stage of labour and that this effect is reversed by the antagonists.

Pethidine alone has an effect on the baby, particularly in dosage over 200 mg, delaying onset of breathing and leading to need for more treatment; this effect is largely abolished by the antagonists. Contrary to general belief the greater effect on the baby occurs when the last dose has been given over three hours before delivery (this can be shown to be statistically significant, $P = 0{\cdot}1 - 0{\cdot}01$). These findings are in line with those of Roberts *et al.* (1957) and Posner (1960).

There were insufficient forceps deliveries, stillbirths and neo-natal deaths in these series for statistical comparison. Similarly the Cæsarean section rate showed no change or any connexion with the use of these drugs.

The number of deliveries in the department has increased from 1,000 in 1952 to 1,500 per annum at present, and the proportion of abnormal cases has also increased. In spite of this there has been no evidence of ill-effects on the baby, nor of increased operative interference. This has been achieved in association with a 40% average increase in dosage of pethidine per case, with correspondingly better analgesia for the mothers (Fig. 1).

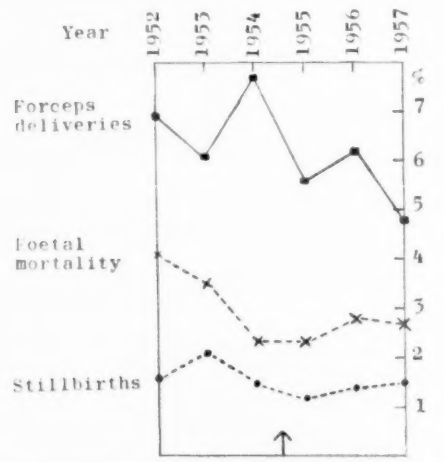

FIG. 1.—Dartford Unit—booked cases. Antagonist started at arrow.

Present Method of Pain Relief in Childbirth

As a result of seven years' study and practice a new method of pain relief in childbirth has evolved, for routine use by midwives, which is based on repeated injections of a pethidine-antagonist mixture. Each dose contains 100 mg of pethidine. The first dose is given at about 2 fingers dilation of the cervix; the second dose one hour later. Further doses are given as required every two to four hours to maintain good analgesia. The anticipated time of delivery is ignored. Later, supplementation is with gas-air, or, when indicated, trilene-air inhalation from an approved apparatus. When additional *sedation* is required, a single injection of a phenothiazine derivative is ordered by the obstetric staff (usually chlorpromazine 50 mg intramuscularly). This is almost invariably for some obstetric abnormality. This method gives excellent results in 40% of all patients, satisfactory results in a further 52%, and only 8% fail to appreciate it. The condition of the babies at birth is better after using high doses of the mixtures than after even low doses of pethidine alone—as at present used by midwives generally (*see* Table I).

Further use of these mixtures is recommended.

REFERENCES

BAKER, F. J. (1957) *Anæsthesia*, **12**, 282.

BARNES, J. (1947) *Brit. med. J.*, i, 124.

BULLOUGH, J. (1955) *Brit. J. Anæsth.*, **27**, 181.

—— (1958) *Acta anæsth. belg.*, **9**, 36.

—— (1959*a*) *Anæsthesist*, **8**, 114.

—— (1959*b*) *Brit. med. J.*, ii, 859.

——, and TOMLIN, P. J. (1959) Report to Assocn. Anæsthetists; Research in Obstetric analgesia; awaiting publication.

ECKENHOFF, J. E., and FUNDERBURG, L. W. (1954) *Amer. J. med. sci.*, **228**, 546.

——, HOFFMAN, G. L. Jr., and FUNDERBURG, L. W. (1953) *Amer. J. Obstet. Gynec.*, **65**, 1269.

NUNN, J. F., and PINCOCK, A. C. (1957) *Brit. J. Anæsth.*, **29**, 98.

PATERSON, S. J., and PRESCOTT, F. (1954) *Lancet*, i, 490.

POSNER, A. C. (1960) *Brit. med. J.*, i, 124.

ROBERTS, H., KANE, K. M., PERCIVAL, N., SNOW, P. and PLEASE, N. W. (1957) *Lancet*, i, 128.

STURROCK, J. (1939) *J. Obstet. Gynæc. Brit. Emp.*, **46**, 428.

DISCUSSION

Dr. R. I. Bodman (Uxbridge) said that the wealth of material presented by Dr. Bullough had left him confused as to his conclusions. Dr. Bullough had not said how the ratio of antagonist to pethidine was determined, nor given any evidence as to whether the doses chosen antagonised only the respiratory depression of pethidine without affecting its analgesic action. The picture was further confused by Dr. Bullough postulating that the antagonist itself had a "narcotic" or analgesic effect.

The method of assessing analgesia employed in this investigation was open to serious criticism. He doubted if the Section should accept evidence on such a difficult subject as analgesia which was based on Dr. Bullough's report of what the nursing staff said the patients felt.

Professor W. W. Mushin (Cardiff) said that Dr. Bullough's results seemed to provide some further information on the vexed question of whether levallorphan antagonized not only the respiratory depressant effects of pethidine, but also its analgesic ones. The fact that substantially larger doses of pethidine in shorter intervals of time were used in his cases than was normally done, seemed to indicate that the reduction of analgesic potency by levallorphan was considerable. Dr. Bullough nevertheless had shown that it was possible to mix levallorphan and pethidine in proportions which left respiratory activity adequate yet provided an acceptable degree of analgesia.

Dr. J. Selwyn Crawford (Leeds) said that Dr. Bullough's well-documented figures represented the third indication (Roberts *et al.*, 1957; Colburn and Salzman, 1960) that infants of mothers who received pethidine or pethidine-levallorphan three to four hours prior to delivery were more likely to be depressed than were those whose mothers received these drugs one-half to two hours before delivery. This response demanded immediate investigation. It might reflect a differential rate of metabolism of the drugs, or possibly a differential rate of return of the two drugs from child to mother.

Little was known of the way in which the depressed fœtus could deal with any drug which it received via the placenta, and the unbridled administration of narcotic-antagonist mixtures during labour must not be encouraged.

Dr. Crawford was disappointed by the continued use of the terms "white asphyxia" and "blue asphyxia". Surely by now anæsthetists should give the lead to clinicians by employing the Apgar scoring system (Apgar, 1953).

At least one phenothiazine derivative (Phenergan) crossed the placenta in appreciable quantities (Crawford, 1960), and Dr. Crawford urged that whenever one of these drugs was administered during labour, precautions should be taken to reduce the concomitant dose of narcotic or to increase the dosage of associated narcotic antagonist.

REFERENCES

Apgar, V. (1953) *Curr. Res. Anesth.*, **32**, 260.

Colburn, D. W., and Salzman, M. (1960) *N.Y. State J. Med.*, **60**, 246.

Crawford, J. S. (1960) To be published.

Roberts, H., Kane, K. M., Percival, N., Snow, P., and Pelease, N. W. (1957) *Lancet*, i, 128.

Dr. Shila Ransom (London) had made tocographic tracings of the effects of the two antagonists on uterine action but no definite change was shown in the few recordings made.

She thought Apgar's method of assessing the condition of the newborn was impractical for a midwife working on her own, as an independent observer with a stop-watch was required.

It was known to psychiatrists that the phenothiazine derivatives might help abnormal patients but make normal ones feel worse. Mothers who wanted to be more or less in possession of their mental faculties might dislike the effect of these drugs. She agreed that the "psychological aspect" was important, but interpreted it to mean supplying some of the patient's basic human needs of encouragement and understanding, not simply administering confusional drugs. What was needed was more efficient *analgesia*, not so much for mothers delivered in hospital, for whom many resources were available, but for those in the care of domiciliary midwives who were restricted in the use of pethidine by statutory regulations. Dr. Bullough had made a valuable survey and although more work still needed to be done on the antagonists, he had shown the possibility of their being the means of midwives being allowed a freer use of pethidine, and of having at their disposal more effective analgesia.

Dr. W. N. Rollason (Aberdeen) said that Dr. Bullough had mentioned that in 20% of his cases extra sedation was required and in these cases he gave 50 mg of chlorpromazine intramuscularly. He did not state whether or not the baby was more depressed in these cases but the literature on this drug has implied that it does not cause fœtal depression. Dr. Crawford, however, said that this drug crossed the placental barrier readily and in fact could depress the fœtus. This accorded with his own limited experience. It would appear that further controlled studies were required before chlorpromazine could be recommended for routine use in obstetrics.

Dr. D. A. Buxton Hopkin (London) said that successful obstetric sedation involved more than the relief of pain by opiates, for many women came to their labour in a highly charged emotional state.

A similar state of tension arising from any other cause would be treated with one of the "tranquillizing" drugs which promoted emotional indifference so that the patient "no longer attends to her environment" (Weiskrantz, 1957). Promethazine, which combined such properties with hypnotic and antiemetic effects, had been used for obstetric sedation for over five years at the Annie McCall and Lambeth Hospitals with gratifying results.

Early in labour amylobarbitone (gr iii) and promethazine (25 mg) had replaced chloral. Distress was relieved and a restful sleep induced in 90% of patients who often woke refreshed with labour well established. The vomiting rate of 25% after chloral was reduced to 3·5%.

When labour was well established the mother received an intramuscular injection of 50 mg promethazine together with 100 mg pethidine. Further

pethidine was given if necessary but the promethazine was not repeated for about six hours.

The records of 500 patients receiving added promethazine were compared with 350 receiving pethidine alone. The added promethazine did not add to the complications of labour in respect of either mother or child.

Acute distress on admission (which was nearly always associated with a first stage of over twenty-four hours) was completely relieved in 90% of patients (total 102) whereas pethidine alone was ineffective in 32 of these women who, however, became calm and relaxed after a subsequent injection of promethazine.

The condition of the infants at birth was consistently better when promethazine was used. Those classified as "poor" constituted only 2% compared with a figure of 6% for those receiving pethidine alone. In this respect promethazine was an effective morphine antagonist with added anti-emetic and sedative properties not possessed by nalorphine and levallorphan.

REFERENCE

WEISKRANTZ, L. (1957) In: Psychotropic Drugs. Eds.: S. Garattini and V. Ghetti. London; p. 67.

Mr. Gilbert Dalley (London) emphasized that Dr. Bullough's method was one which could safely be used by midwives on their own initiative; they were at present restricted to 200 mg of pethidine. From clinical observation (this work was done in his unit) he could support the statement that babies born to mothers who had been given antagonist mixtures did not suffer from respiratory depression. In some places, antenatal education might be deficient leading to tension and fear in the unprepared mother, who consequently needed sedation as well as analgesia. But education was not the complete answer, as hitherto enthusiastic disciples of the Dick-Read method frequently found: because this depended on a personal fixation on the obstetrician and was so time consuming that it was not a practical proposition for hospital patients.

Dr. Bullough, in reply to Dr. Bodman, said that his present conclusions were that antagonists should be added to pethidine in the least amount to neutralize respiratory depression when the mixture was given intramuscularly and that this mixture could be used freely throughout labour to maintain good pain relief without endangering the baby. The methods of finding such mixtures had been described. The weak narcotic action of nalorphine had been described by others, e.g. Eckenhoff and Funderburg (1954). The method of assessing obstetric analgesia was the same as used by other workers; over 300 of the cases were observed and assessed by doctors (Baker, 1957; Bullough and Tomlin, 1959). He knew of no more satisfactory method.

In reply to Professor Mushin: If excess antagonist were given there might be loss of analgesia. In the ratios described there was no evidence of loss of overall analgesic and sedative effect, rather the opposite. Higher dosage of the mixtures had been used as definite policy to produce better results for the mothers. The dosage in mg per hour had not actually increased. His findings were in line with those of Roberts *et al.* (1957).

In reply to Dr. Crawford: The term "white asphyxia" was still widely employed. In obstetrics the term asphyxia, anoxia, shock and depression were habitually used to describe the same condition, as the precise cause was often unknown at the time. He agreed with Dr. Ransom's criticism of the Apgar rating.

In reply to Dr. Rollason: He did not recommend the routine use of phenothiazine drugs in normal cases at present. They were ordered by the obstetricians for obstetrically abnormal cases, most commonly hypertension, toxæmia, and some forms of inertia. Additional sedation was not usually required in normal cases. At present he could not say what effect chlorpromazine had on the baby.

In reply to Dr. Hopkin: Dr. Hopkin's clinical material at Lambeth was quite different, apparently, from that at Dartford; thus any findings were not comparable without selecting cases. Dr. Bullough had suggested to his colleagues the use of promethazine in certain types of case, but they appeared to prefer chlorpromazine. Using the respiratory methods described earlier he had so far been unable to show that promethazine had any effect in the prevention or correction of pethidine-induced respiratory depression. Any beneficial effect on the baby would be due to some other mechanism.

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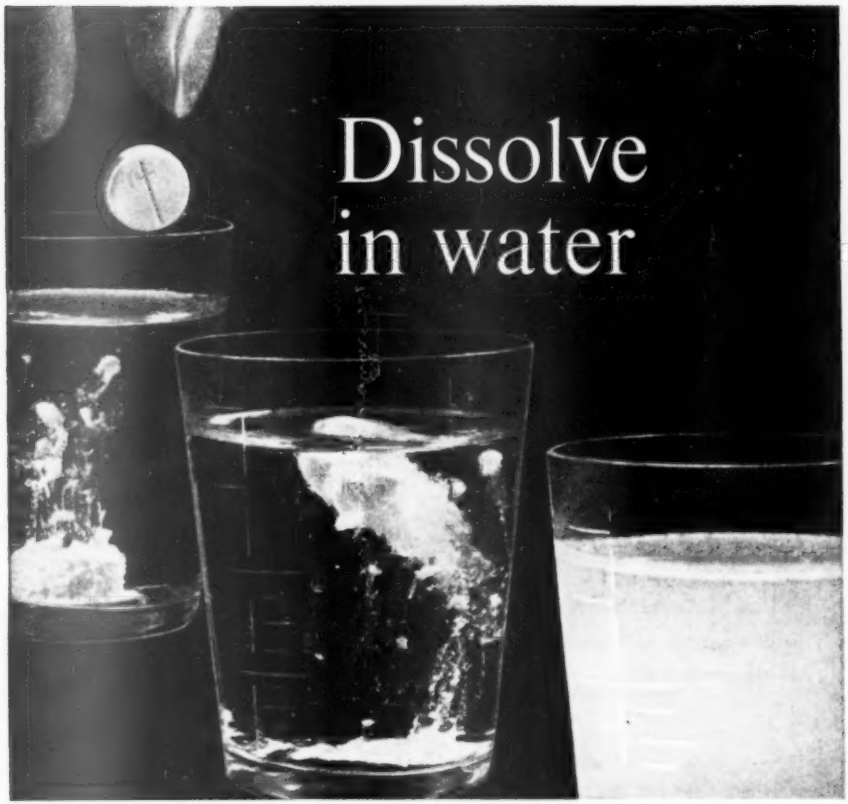

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HERITABLE DISORDERS OF CONNECTIVE TISSUE

Dr. J. G. Parish (Durham):

Skeletal Syndromes Associated with Arachnodactyly

In 1896 Antoine Marfan described a musculoskeletal disorder in a 5-year-old girl producing excessive lengthening and slenderness of the arms and legs. The fingers were flexed by fibrous contractures and resembled the legs of a spider. He called the condition "dolichosténomélie" (long narrow limbs). Méry and Babonneix (1902), in a later report on the same patient, described the development of further skeletal defects, namely, a funnel chest, outward splaying of the lower ribs, and a marked dorsal kyphoscoliosis. Achard (1902) found a somewhat different skeletal picture in his patient. Although the fingers were excessively slender, they were virtually normal in length and hypermobile. He suggested the name arachnodactyly.

The classical triad of arachnodactyly, cardiac and ocular abnormalities, which constitutes Marfan's syndrome, was not fully described until some years later. Cardiac abnormalities were related to the syndrome by Salle (1912) and congenital eye defects by Boerger (1914). Recent estimates of the incidence of cardiovascular changes vary from 17·5% (Sinclair, 1958) to 65% (Lynas, 1958), depending on the criteria adopted for the diagnosis of arachnodactyly and the source of the material. Similarly, the incidence of ocular defects varies from 45% (Sinclair, 1958) to about 75% (Ross, 1949). These differences reflect a tendency for patients with milder degrees of arachnodactyly to be referred to rheumatic or orthopædic clinics with skeletal defects only, while the more severe forms present at cardiac or ophthalmic clinics. Family surveys of patients with the complete syndrome indicate the inheritance of a single irregular dominant autosomal gene. Incomplete forms of the syndrome (*formes frustes*) are often found amongst other members of the family. There is some evidence that the gene for Marfan's syndrome may produce more severe results in a subject of asthenic type; on the other hand, mating with a partner of pyknotic build may result in less marked changes in the offspring (Lynas, 1958).

The only consistent pathological finding in Marfan's syndrome is a degeneration in the walls of the aorta and pulmonary artery with necrosis and fragmentation of elastic fibres, disorganization of smooth muscle fibres and the appearance of cystic areas rich in mucopolysaccharides. McKusick (1956) suggested that the basic disorder is a constitutional inadequacy of the elastic fibres.

Methods of Estimating Arachnodactyly

Achard (1902) was the first to investigate arachnodactyly using measurements of radiographs of the hands. He found that the metacarpals, and the proximal and middle phalanges were of normal length, but that measurements of the width of the phalanges in arachnodactyly showed a definite slenderness of the middle of the shafts of these bones. In contrast, the epiphyses were normal in width, resulting in a knobbly appearance of the corresponding joints. He also noted that the distal phalanges were elongated but this is not a constant finding. Sinclair (1960) has recently devised a method of estimating the relative slenderness of the metacarpal bones from measurements of radiographs by means of the metacarpal index (*see* Fig. 1).

The RELATIVE SLENDERNESS of ONE METACARPAL

$$= \frac{\text{LENGTH of METACARPAL}}{\text{BREADTH at MIDPOINT}}$$

The METACARPAL INDEX

$$= \frac{RS_2 + RS_3 + RS_4 + RS_5}{4}$$

where RS_2, RS_3, RS_4, RS_5 are the values of the relative slenderness of the 2nd, 3rd, 4th and 5th metacarpals.

FIG. 1.—Metacarpal index.

The relative slenderness of one metacarpal is estimated by measuring the length of the metacarpal and dividing this by the breadth of the metacarpal at the *exact midpoint*. The metacarpal index is estimated by averaging the relative slenderness of the 2nd, 3rd, 4th and 5th metacarpals.

I have found that the phalangeal index for the ring finger is the most likely to be abnormal in arachnodactyly, and have therefore selected this index for the purpose of this paper. The phalangeal index for any one proximal phalanx

(Fig. 2) is obtained by estimating the axial length of the proximal phalanx and dividing by

$$\frac{\text{Axial length of one proximal phalanx}}{\text{Minimal width of shaft of the same proximal phalanx}}$$

FIG. 2.—Phalangeal index.

the *minimal* width of the shaft. The measurements were made with a Perspex ruler with estimates of the length of the bones to the nearest millimetre and width to the nearest half millimetre.

Measurements of the Normal Hand

Postero-anterior radiographs of both hands were done on a consecutive series of patients aged 21 to 45 years attending for the first time the physical medicine outpatient clinics of the Durham group of hospitals. The range of passive hyperextension of the metacarpal phalangeal joints was also recorded. This survey is not yet complete, but to date readings for 26 men and 53 women are available (*see* Table I). Both the

TABLE I.—NORMAL VALUES OF METACARPAL AND PHALANGEAL INDICES

		No. of subjects	Mean	Range
Metacarpal index				
Men:	Right hand	26	6·8	5·9–7·6
	Left hand		7·0	6·0–8·0
Women:	Right hand	53	7·7	6·3–8·9
	Left hand		7·8	6·8–9·0
Phalangeal index for ring finger				
Men:	Right hand	26	4·1	3·6–4·5
	Left hand		4·1	3·7–4·6
Women:	Right hand	53	4·7	4·0–5·4
	Left hand		4·7	4·0–5·6

metacarpals and phalanges are distinctly more slender in women than in men. In addition, there is a slight tendency for the bones of the left hand to be more slender than those of the right in both sexes.

Measurements of the Hand in Marfan's Syndrome

There is a slight overlap in the range of bone measurements of the normal hand and in Marfan's syndrome. In one female patient with the complete syndrome the metacarpal index was 8·7 (right hand) and 8·6 (left hand), and the phalangeal index for the ring finger, 5·8 (right hand) and 5·4 (left hand). Only the phalangeal index for the right ring finger was above the normal range. This patient also showed a reversal of the usual tendency of the bone

FIG. 3.—Marfan's syndrome: slender metatarsals and metatarsus quintus valgus.

indices to be higher in the left hand than the right. Several other abnormalities were also more pronounced on the right side of the body including recurrent subluxation of the patella and ankle-joint, metatarsalgia associated with increased slenderness of the metatarsals in the right foot and ligament laxity (Fig. 3), and the eye changes. The cardiac lesion presented as a dilatation of the ascending aorta observed on screening. The lengths of the metacarpals and phalanges corresponded to those of a normal person of the same height. Patients with severe cardiac lesions usually show more marked arachnodactyly with increased lengths of the metacarpals and phalanges beyond the normal range and a metacarpal index up to 11 (Sinclair, 1960). Incomplete forms of the syndrome may show indices within the normal range.

Skeletal Syndromes associated with Arachnodactyly (Slender Fingers)

Marfan's syndrome.—The principal skeletal abnormalities which may be observed in this syndrome, together with the date of the original description, are shown in Table II. Changes occasionally described include synostosis of ribs and distal tibia and fibula, anomalies of vertebral ossification, defects of the sacrum and distortion of the pelvis.

Arachnodactyly with mandibulofacial dysostosis

TABLE II.—PRINCIPAL SKELETAL MANIFESTATIONS OF MARFAN'S SYNDROME

	Author
General characteristics	
Increased length and slenderness of limbs most marked in hands and feet; sparse subcutaneous fat; poor muscular development; fibrous tendon contractures	Marfan (1896)
Ligament laxity	Achard (1902)
Span greater than height by 2 to 5 in. (5 to 12·5 cm)	
"Pubis to heels" greater than "pubis to vertex" by 2 to 6 in. (5 to 15 cm)	
Hands	
Metacarpals and phalanges may be normal in length but are excessively slender	Achard (1902)
Webbing of fingers	Thomas (1914)
Lower limbs	
Dislocation of hip-joints (dislocation of many other joints and of patella described subsequently)	Dubois (1912)
Genu recurvatum	Boerger (1914)
Genu valgum	
Small high mobile patella	Méry and Babonneix (1902)
Distance from lower border of patella to tibial tuberosity over 1·8 in. (4·6 cm)	Booth *et al.* (1957)
Contracture of feet and hammer toes; posterior projection of calcaneum	Marfan (1896)
Pes planovarus	Poynton (1903)
Webbed toes	
Trunk	
Funnel chest; kyphoscoliosis; outward splaying of lower ribs	Méry and Babonneix (1902)
Pigeon chest	Thursfield (1920)
Winged and boat-shaped scapula	Boerger (1914)
Dolichocephaly	Marfan (1896)
Prominent supraorbital ridge	Ormond and Williams (1924)
Prognathism	Duperie *et al.* (1921)
Melancholy facial expression	Boerger (1914)
High arched palate	Poynton (1903)
Deformity of ears; large or peaked auricles; abnormalities of conchæ	Poynton (1903); Thomas (1914)

(*Achard's syndrome*).—When Thursfield reviewed the literature on Marfan's syndrome in 1920, he remarked that the skeletal picture in Achard's cases differed from the rest and doubted that they belonged in the same category. I recently had a female patient, aged 40, whose appearance

FIG. 4.—Achard's syndrome: micrognathism.

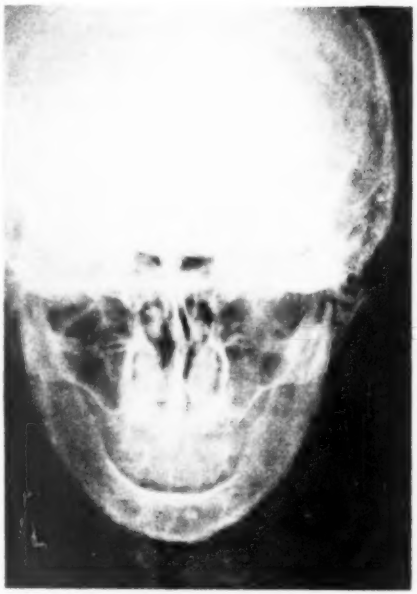

FIG. 5.—Achard's syndrome: dysostosis of mandible.

FIG. 6.—Achard's syndrome: short mandibular rami with increased angle of jaw.

was similar to Achard's description, with the following differences from the classical skeletal changes in Marfan's syndrome:

(1) The skull is broad, brachycephalic (cephalic index 83·5) and contrasts strangely with the smallness of the lower part of the face and mandible (Fig. 4). X-rays show an abnormally small mandible (Figs. 5 and 6).

(2) Bone changes are confined entirely to the hands and feet in spite of well-marked arachnodactyly (metacarpal index 10·6, right; phalangeal index for right ring finger 6·8). The span (64 in.—162·5 cm) is less than the height (65 in.—165 cm).

(3) Ligament laxity is also confined to the hands and feet. The length of the infrapatellar tendon lesion is within normal range (Booth *et al.*, 1957).

(4) The muscles are well developed, the maximal calf circumference being 14½ in. (37 cm). There is abundant subcutaneous fat especially around the joints.

I was unable to discover any ocular or cardiac abnormalities in this patient, but Calmettes *et al.* (1955) report a similar case with ventricular septal defect and bilateral lens dislocations. They also describe a patient with brachydactylia, lens dislocation and a similar mandibulofacial dysostosis, and remark on the similarity between the two syndromes. Lambie *et al.* (1950) suggest that such variations in the skeletal picture are due to disturbances of genetically determined time factors, concerned with the orderly sequence of growth of mesenchymal tissues.

Status Bonnevie-Ullrich and osteogenesis imperfecta.—It may seem strange to include two conditions in which the metacarpals and phalanges are shorter than normal in a discussion of arachnodactyly. In both these conditions, however, some of the bone measurements indicate the presence of the excessive slenderness of the shafts, characteristic of arachnodactyly. Ligament laxity also occurs in these syndromes and may be linked with the bone slenderness. In status Bonnevie-Ullrich many of the skeletal changes are common to Turner's syndrome, including webbing of the neck, but gonadal dysgenesis is absent (Zorab and Jackson, 1955; Ginorio, 1956). Achard's syndrome may form a link between the long-finger and short-finger syndromes, suggesting that these disorders may be closely associated on a genetic basis[1].

Conclusions

Although the classical triad of Marfan's syndrome is rare, modified forms presenting with skeletal deformities are relatively common. The distinction between these patients and normal patients with long fingers is often difficult, since ligament laxity and spinal deformities occur in both groups. The metacarpal and phalangeal indices are of value in deciding whether a congenital mesodermal dystrophy is present.

The syndrome is likely to become more common as a greater number of patients survive into adult life with improved medical care. Patients with the modified forms are potential carriers of genes, which may be responsible for congenital heart disease and congenital eye lesions in their offspring. The bone indices may help in determining whether a case of congenital heart disease with arachnodactyly has arisen *de novo* as a mutation, or has been inherited from one of the parents. In the latter case other members of the family may be affected.

Acknowledgments.—I am grateful to Dr. R. J. G. Sinclair, Rheumatic Unit, Edinburgh, and Dr. A. N. Zinovieff for assistance in the preparation of this paper and to Dr. G. T. Holroyd, Mr. K. Watson and Miss R. Shotton for the illustrations.

[1]In this connexion Bowers (1959) has described the occurrence of patients with the Weill-Marchesani syndrome in a family exhibiting the Marfan trait.

REFERENCES

ACHARD, M. C. (1902) *Bull. Soc. méd. Hôp. Paris*, **19,** 834.

BOERGER, F. (1914) *Mschr. Kinderheilk.*, **13,** 355.

BOOTH, C. C., LOUGHRIDGE, L. W., and TURNER, M. D. (1957) *Brit. med. J.*, ii, 80.

BOWERS, D. (1959) *Ann. intern. Med.*, **51,** 1049.

CALMETTES, L., DEODATI, F., MEALE-BERAL, J., and AMALRIC, P. (1955) *Oto-Neuro-Ophtal. Rev.*, **27,** 488.

DUBOIS, M. (1912) *Ann. Soc. méd.-chir. Liège*, **12,** 896.

DUPÉRIÉ, R., DUBOURG, E., and GUÉNARD, F. (1921) *J. Med. Bordeaux*, **92,** 43.

GINORIO, A. R. (1956) *J. Bone Jt. Surg.*, **38A,** 885.

LAMBIE, C. G., SHELLSHEAR, K. E., and SHELLSHEAR, J. L. (1950) *Med. J. Aust.*, i, 213.

LYNAS, M. (1958) *Ann. hum. Genet., Lond.*, **22,** 289.

MCKUSICK, V. A. (1956) Hereditary Disorders of Connective Tissue. St. Louis.

MARFAN, A. B. (1896) *Bull. Soc. méd. Hôp. Paris*, **13,** 220.

MÉRY, H., and BABONNEIX, L. (1902) *Bull. Soc. méd. Hôp. Paris*, **19,** 671.

ORMOND, A. W., and WILLIAMS, R. G. (1924) *Guy's Hosp. Rep.*, **74,** 385.

POYNTON, F. C. (1903) *Trans. med. Soc. Lond.*, **26,** 338.

ROSS, L. J. (1949) *Amer. J. Dis. Child.*, **78,** 417.

SALLE, V. (1912) *Jb. Kinderheilk.*, **75,** 540.

SINCLAIR, R. J. G. (1958) *Bull. Rheum. Dis.*, **8,** 153.

—— (1960) *Quart. J. Med.*, **29,** 19.

THOMAS, E. (1914) *Z. Kinderheilk.*, **10,** 109.

THURSFIELD, H. (1920) *St. Bart's Hosp. Rep.*, **53,** 35.

ZORAB, J. S., and JACKSON, E. P. (1955) *Guy's Hosp. Rep.*, **104,** 258.

Dr. C. D. Calnan (London):

Klemperer and his colleagues coined the term "diffuse collagen disease" as a title for their paper (Klemperer *et al.*, 1942), in which they suggested that scleroderma and systemic lupus erythematosus be regarded as primary affections of the connective tissue. The concept of collagen disease rapidly spread and became an acceptable diagnostic label. Klemperer's original purpose had been to focus attention on collagen and connective tissue in the pathogenesis of disease, and in 1950 he warned "the impatience of clinical investigators and a peculiar worship of diagnostic terms have led to an exaggerated popularity of the diagnosis of Collagen Disease. There is a danger that it may become a catch-all term for maladies with puzzling clinical and anatomical features. It is not a term applicable to diagnosis and certainly does not define the morbid process of the diseases grouped together".

This paper is principally concerned with the dermatological manifestations and pathogenetic processes of heritable connective tissue disorders. Marfan's disease has been fully discussed by Dr. Parish (1960). Apart from the skeletal and cardiovascular changes, gynæcomastia and a relative lack of subcutaneous fat may be noted, but the skin is otherwise normal. In one patient (Storck, 1952; Haber, 1959) a peculiar (probably congenital) localized anomaly of elastic tissue was present on the neck—elastoma intrapapillare perforans verruciforme, sometimes referred to as Miescher's elastoma. The nature and ætiology of the latter condition is unknown, but one patient with it subsequently died of a dissecting aneurysm of the aorta (Anning, 1958), which suggests that there may be an associated abnormality of the elastica of blood vessels. The most fascinating aspect of the Marfan syndrome, however, is the finding that similar skeletal changes and dissecting aortic aneurysm can be produced experimentally in rats fed with β (γL-glutamyl) aminoproprionitrile, found in the seed of *Lathyrus odoratus* (Ponseti and Baird, 1952).

In osteogenesis imperfecta the skin is thin and superficial vessels are visible. Blue sclerotics, gaping scars after trauma, and occasionally purpura are other features. Blegvad and Haxthausen (1921) described a case associated with macular atrophy of the skin and a zonular cataract. The connective tissue defect in this disorder is thought to be a failure of maturation and organization of collagen, although the shrinkage temperature coefficient of collagen in the skin is normal (Follis, 1953).

Cutaneous changes are not a prominent feature of the Hurler syndrome (gargoylism, lipochondrodystrophy), although the skin tends to be rough and coarse and an excess of lanugo (hypertrichosis lanuginosa) may be seen. There is no unanimity as to whether this syndrome should be regarded as a disorder of collagen, mucopolysaccharide, or lipoid.

Pseudoxanthoma elasticum, like lupus erythematosus and scleroderma, is now recognized as a systemic disorder with prominent presenting manifestations in the skin.

The abnormality rarely reveals itself before puberty; the case reported by Wolff *et al.* (1952) is a notable exception. In the early stages and in mild cases it is easy to miss the skin lesions. The abnormal patches of skin are smooth, but comprise aggregations of pale yellowish or biscuit coloured soft flat papules. In more marked examples the normal lines of the skin are very prominent, as though thrown up in relief, and the clinical appearance imitates that of the senile, solar, or so-called sailors' skin, although the pathology is different. In more severe cases the skin becomes loose and folded, sometimes to a remarkable degree. The sites of election are the back and sides of the neck, axillæ, groins, knee and elbow flexures, and around the umbilicus; occasionally it is very extensive over the whole neck, abdomen, and large areas of the trunk and limbs; mucosæ may be involved. The histology of the skin lesion is diagnostic, but in mild cases very careful examination of the slides is required. In a hæmatoxylin and eosin section the changes may pass unnoticed, but stains for elastic tissue will reveal localized areas of disorder and fragmentation of the elastica; and a von Kossa stain shows a surprising amount of calcium deposition in the areas. Rarely is this calcium evident clinically or radiographically, although Gold (1951) described a patient whose lesions ulcerated and discharged the calcium (and who incidentally suffered from Still's disease). The deposit appears to be purely a secondary imbibition by the abnormal elastic fibres since no change in systemic calcium metabolism is detected. It is probably analogous to deposits in degenerative vascular disorders (atherosclerosis, Monkeberg's sclerosis).

Although present in a case described by Chauffard (1889) the close association of eye changes with the skin was first emphasized by Grönblad (ophthalmologist) and Strandberg (dermatologist) in 1929, and the condition is often referred to as the Grönblad-Strandberg syndrome. Ocular lesions are of two types, angioid streaks and a choroidoretinitis. The

former are diagnostic; they are wider than the retinal vessels; paler, but radiate out like the vessels. The choroidoretinitis exudate and organizing hæmorrhages are less specific but are the cause of ocular symptoms, usually deterioration of vision. Little is known of the pathogenesis of the eye changes, although the angioid streaks are probably caused by breaches in the elastic lamina of Bruch's membrane, and the choroidoretinitis is considered secondary to a vascular lesion.

Most recent interest in pseudoxanthoma elasticum, however, centres round the evidence of a generalized defect of the elastica of blood vessels. Numerous examples of hæmorrhage from the gastro-intestinal tract, lungs and uterus, besides other organs, are now known, even though their significance may not have been appreciated at the time. Spontaneous hæmarthrosis may occur. Peripheral arteries in the limbs are also involved —a fact which may have diagnostic significance, even if symptoms such as intermittent claudication are rare. Carlborg (1944) found a reduced pulse wave in 14 out of 51 affected patients. Diminution or absence of a dicrotic notch may be very striking, and it makes one feel that oscillography should be used more frequently by the clinician. It is possible that this particular abnormality of the elastica of vessels may be responsible for some examples of unexplained hæmoptysis, hæmaturia, menorrhagia, and gastro-intestinal hæmorrhage in the absence of skin or eye lesions. In one of two children with gastric bleeding described by Edwards (1959), the skin, on careful scrutiny by a dermatologist (Marten, 1960), showed no clinical lesions of pseudoxanthoma elasticum. Biopsies from the skin of the neck and axilla however, showed deposition of calcium around elastic fibres which were a little fragmented. In another patient, a pulmonary lobe removed because of hæmoptysis revealed vascular changes identical to those found in pseudoxanthoma (Marten, 1960).

Professor K. R. Hill has found vascular lesions with similar histology in the horse and some other animals. In the horse plaques of the abnormal tissue are seen on the surface of the endocardium and aorta, and it is interesting to remember that the first case of pseudoxanthoma described (Balzer, 1884) showed, at autopsy, such patches on the atrial and ventricular endocardium and pericardium. McKusick (1956) also has recorded such cardiac lesions, and Hill (1959) has found them in the atrium and arteries of a patient who died following hæmorrhage from a gastric ulcer, but without known evidence of pseudoxanthoma. A special awareness of these changes on the part of morbid anatomists may prove rewarding.

The controversy over whether pseudoxanthoma elasticum represents a disorder of collagen or elastic tissue illustrates the inadequacy of our present techniques. Tunbridge *et al.* (1952) believe that the differences between collagen and elastica may be more apparent than real, since they found that the dystrophic fibres in pseudoxanthoma have the electron microscopic appearances of collagen.

It is accepted that fibres with the tinctorial properties of elastica may not necessarily be elastic tissue, the classic example being the common senile or solar elastosis seen in the upper parts of the dermis. Many workers, however, state that collagen fibres are normal in pseudoxanthoma, and that the abnormal fibres are specifically removed by elastase (Findlay, 1954; Moran and Lansing, 1958). It is essential to have as pure a preparation of the enzyme as possible, and to show that it has no action on collagen. No views have yet been advanced as to the precise defect in these patients' elastic tissue responsible for its weakness.

The Ehlers-Danlos syndrome or cutis hyperelastica is, again, a disorder which is now attracting the attention of many physicians other than dermatologists. It is a congenital and familial mesenchymal dysplasia, the principal features of which are hyperelasticity of the skin, hyperextensibility of joints, and skin friability giving rise to atrophic papyraceous scars after trauma, especially over prominences such as the knees, elbows, and knuckles. Important lesser characteristics are molluscoid cyst-like tumours of connective tissue, and small dermal nodules or spherules consisting of fat, which may become calcified (Weber and Atkinson, 1938). An additional association is purpura and bruising, symbols of the defective vascular elastic tissue. They may even be presenting features in minor or incomplete examples of this syndrome (Sneddon, 1957). Meara (1958) described such a patient, who also had a lesion of another congenital dystrophy of elastic tissue, Miescher's elastoma perforans verruciforme (referred to above). A variety of internal lesions have been described in Ehlers-Danlos patients, such as diaphragmatic hernia and eventration, dissecting aortic aneurysm, spontaneous lung rupture, and gastro-intestinal diverticula.

There is no characteristic or accepted histological change in the skin or other organs to account for this disorder. Examination of the

skin with the light microscope and electron microscope have not revealed any gross abnormalities of the collagen or elastic tissue. Jansen (1955) has put forward the most attractive hypothesis for the pathogenesis at the present time. He says that the connective tissue fibres are normal biochemically at the molecular level, but that their arrangement at the biomolecular level, i.e. their organisation into adult tissue, is abnormal. He described it as "defective wickerwork" of collagen, although the elastic tissue is probably normal. What mechanisms are responsible for the organisation of tissue are not known; they may or may not be enzymic. An unconfirmed observation is the finding in two patients with Ehlers-Danlos syndrome of a greatly increased concentration of normal serum elastase inhibitor (Hall *et al.*, 1955).

McKusick (1956) lists other conditions which he regards as possible or probable heritable anomalies of connective tissue. A few are of dermatological interest such as neurofibromatosis, epidermolysis bullosa, mastocytosis (urticaria pigmentosa), Miescher's elastoma, connective tissue nævus (cobblestone or pavement nævus), and adenoma sebaceum (epiloia or tuberous sclerosis). The abnormality in epidermolysis bullosa is a weakness of epidermodermal adhesion. Gentle heat or repeated stretching can break this junction, but separation can also be readily achieved with elastase (or crude trypsin containing elastase). This suggests that the sub-epidermal garland of elastic fibres is the main adhesive agent between dermis and epidermis, and it is possible that these fibres are congenitally weak in patients with epidermolysis bullosa. The defect would be qualitative rather than quantitative, since histological examination shows substantially normal tissue. No internal connective tissue changes are associated with it.

Localized congenital and familial connective tissue nævus in the skin is recognizable as a morphologically abnormal area of skin, but frequently no abnormality of the dermal tissues can be detected histologically. A more widespread form of it has been described as "collagénome éruptif" (Duverne *et al.*, 1955; Lowenthal, 1957; Calnan and Haber, 1958). These conditions have been inadequately studied to date, but they offer a ready source of material. The same is true of adenoma sebaceum (epiloia). This name is an unfortunate misnomer, and distracts from the essential defect. Almost all patients with this heritable disorder show some sign of a connective tissue nævus (the so-called shagreen patch) over the lumbar area. The whole syndrome may be regarded as a connective tissue abnormality, whether the lesions are in the skin, the eyes, the brain, or in internal organs.

The most striking feature which all these disorders have in common is a qualitative defect in connective tissue. There is little or no evidence that the abnormality is in the molecular structure or microscopic appearances; rather it appears to be in between, at the biomolecular level, in the organization and arrangement of macromolecules into tissue. Professor W. T. Astbury of Leeds has pioneered this field of research. Problems of connective tissue have something in common with keratin; they both belong to the K-E-M-F group of fibrous proteins, widely utilized throughout the animal kingdom. Defects in organization of keratin at the biomolecular level are probably responsible for psoriasis and ichthyosis. Swanbeck (1959) has produced biophysical evidence that in ichthyosis the bundles of 5–10 tonofilaments are aggregated into two or three small, instead of a single large, keratin fibril of 250 Ångström units; in psoriasis the aggregation of tonofilaments has completely failed. Variations in the organizational arrangement of keratin fibrils determine the difference in types of scalp hair in man as much as that of wool in sheep. The growth pattern of the curly hair of the negro or of ingrowing hairs on the male beard cannot be altered permanently. The hair follicles can only produce one particular type of hair. Wool research workers have made great advances in this field and revealed the structural differences between ordinary and angora wool, and have a fairly complete understanding of how keratin molecules are compounded into definitive bundles.

Analogous contributions have been made by the leather industry on the structure of collagen.

Knowledge of the complete amino-acid sequence in the structure of collagen, the details of the organization of collagen molecules into fibrils and bundles and the tissue culture of abnormal connective tissue are three promising lines of research into the problems of the heritable disorders of connective tissue.

REFERENCES

ANNING, S. T. (1958) *Proc. R. Soc. Med.*, **51,** 932.

ASBOE-HANSEN, G. (1954) Connective Tissue in Health and Disease. Copenhagen.

BALZER, F. (1884) *Arch. Physiol. norm. path.*, **4,** 65.

BLEGVAD, O., and HAXTHAUSEN, H. (1921) *Brit. med. J.*, ii, 1071.

CALNAN, C. D., and HABER, H. (1958) *Brit. J. Derm.*, **70,** 261.

CARLBORG, U. (1944) *Acta med. scand.*, Suppl. **151,** 1.

CHAUFFARD, A. (1889) *Bull. Soc. méd. Hôp. Paris*, **3,** 412.

DUVERNE, J., COUDERT, J. O., and COLOMB, D. (1955) *Ann. Derm. Syph., Paris*, **82,** 160.

EDWARDS, H. C. (1959) Proceedings of the World Congress of Gastroenterology. Baltimore; **2,** 819.

FINDLAY, G. H. (1954) *Brit. J. Derm.*, **66,** 16.

FOLLIS, R. H. J. (1953) *Bull. Johns Hopk. Hosp.*, **93,** 386.

GOLD, S. C. (1951) *Postgrad. med. J.*, **27,** 577.

GRÖNBLAD, E. (1929) *Acta ophthal. Kbh.*, **7,** 329.

HABER, H. (1959) *Brit. J. Derm.*, **71,** 85.

HALL, D. A., KEECH, M. K., REED, R., SAXL, H., TUNBRIDGE, R. E., and WOOD, H. J. (1955) *J. Geront.*, **10,** 388.

HILL, K. R. (1959) Personal communication.

JANSEN, L. H. (1955) *Dermatologica, Basel*, **110,** 108.

KLEMPERER, P. (1950) *Amer. J. Path.*, **26,** 505.

——, POLLACK, A. D., and BAEHR, G. (1942) *N.Y. St. J. Med.*, **42,** 2225.

LOEWENTHAL, L. J. A. (1957) *Dermatologica, Basel*, **114,** 81.

MCKUSICK, V. A. (1956) Heritable Disorders of Connective Tissue. St. Louis.

MARTEN, R. H. (1960) Personal communication.

MEARA, R. H. (1958) *Trans. St. John's Hosp. derm. Soc., Lond.*, **40,** 72.

MORAN, T. J., and LANSING, A. I. (1958) *Arch. Path., Chicago*, **65,** 688.

PARISH, J. G. (1960) *Proc. R. Soc. Med.*, **53,** 515.

PONSETI, I. V., and BAIRD, W. A. (1952) *Amer. J. Path.*, **28,** 1059.

SNEDDON, I. B. (1957) *Acta derm-venereol., Stockh.*, **37,** 296.

STORCK, H. (1952) *Dermatologica, Basel*, **104,** 321.

SWANBECK, G. (1959) *Acta derm-venereol., Stockh.*, **39,** Suppl. 43, p. 1.

TUNBRIDGE, R. E., TATTERSALL, R. N., and HALL, D. A. (1952) *Clin. Sci.*, **11,** 315.

WEBER, F. P., and ATKINSON, F. R. B. (1938) *Brit. J. Derm.*, **50,** 267.

WOLFF, H. H., STOKES, J. F., and SCHLESINGER, B. E. (1952) *Arch. Dis. Childh.*, **27,** 82.

Dr. J. S. Lawrence (Manchester):

There must be few tissues in the body which are not liable to be affected adversely on occasion by genetically determined defects. In this respect, the connective tissues excel for there is scarcely a disease of this system in which some evidence of increased familial incidence has not been reported.

Rheumatoid Arthritis

In rheumatoid arthritis, there is evidence of an increased familial incidence of clinical disease from a number of studies (Short *et al.*, 1952; Stecher *et al.*, 1952; Lewis-Faning, 1950; Miall, 1955; Neri, Serneri and Bartoli, 1956). The prevalence varies greatly in different studies but the female relatives always have more than the males.

When, however, a random population sample is examined for clinical, radiological and serological evidence of rheumatoid arthritis, a curious fact emerges: whereas clinical evidence of the disease is two-and-a-half times as common in females, radiological and serological evidence shows no sex difference (Kellgren and Lawrence, 1956). This is because females more often have clinical disease without the other two features and males more often have radiological changes or a positive sheep-cell agglutination test without clinical evidence of the disease.

If now the families of persons with either clinical disease or a positive sheep-cell agglutination test or both are examined (Lawrence and Ball, 1958), certain familial differences emerge. Members of the sero-positive families more often have a positive sheep-cell agglutination test than the controls, no matter whether the propositus had clinical rheumatoid arthritis or not, but members of the sero-negative families have no more positive sheep-cell tests than the controls. Clinical disease on the other hand, is more common in the families of propositi with clinical disease regardless of whether the propositi were sero-positive or sero-negative, but the families of those without clinical disease have roughly the same amount as the controls. A similar pattern has been observed by Bremner *et al.* (1959) in a family study in Edinburgh.

Of 17 spouses of rheumatoid subjects in the study of Lawrence and Ball, none had clinical or radiological evidence of the disease and only one had a positive sheep-cell agglutination test, no more than would be expected by chance. Nor was clinical disease found to be more common in spouses of rheumatoid subjects in a large survey of rheumatic complaints carried out earlier. A genetic cause of the increased familial incidence would thus seem more probable. If so, it would seem that at least two genes are involved.

Since clinical disease is two-and-a-half times as common in females as in males, it may be considered whether one gene is inherited as a sex-linked dominant on the X chromosome. If this were so, it would be passed by affected mothers equally to their sons or daughters but by affected fathers only to their daughters. In Stecher's (1953) series, there were 5 male propositi with affected fathers and this would appear to disprove such an inheritance.

The inheritance of the rheumatoid serum factor is by no means straightforward. Examination of the sheep-cell titre in a random sample of 2,119 persons aged 15 and over in Leigh and Wensleydale, by Dr. J. Ball, has revealed a striking relationship to age (Fig. 1). In the 15–24 age group, only 1% of the population had a positive test. With increasing age, the proportion of positives rose in stepwise fashion to a maxi-

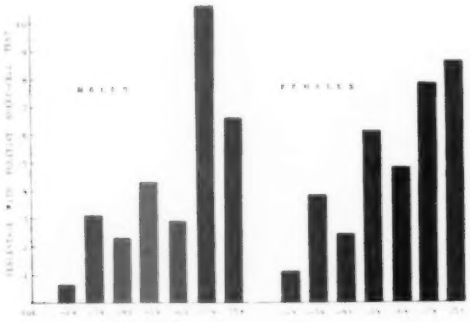

FIG. 1.—Age and sex distribution of positive sheep-cell test in a mixed urban-rural population.

mum of 11% in males and 9% in females in the 65–74 and 75+ age groups respectively. In a group of 100 Nigerian school children, whose sera, collected by Dr. B. S. Blumberg of the National Institute of Health, were examined in another context, no positives were encountered. It would appear, therefore, that the rheumatoid factor is not inherited as such, but results from some metabolic shift. In this, not only a genetic but also an environmental factor would seem to play a part, for it has been found that identical twins may show wide differences in titre.

It is unlikely that even the rheumatoid serum factor is controlled by a single gene, since the sheep-cell titre in population samples is a continuous variable (Kellgren and Lawrence, 1956). Moreover, discrepancies are encountered between different serological tests for rheumatoid factor in the serum (Valkenberg and Ball, 1960). The latex or bentonite test, for example, may be strongly positive in a patient with a negative sheep-cell agglutination test, and the reverse sometimes occurs.

Juvenile rheumatoid arthritis or Still's disease is less often associated with a positive sheep-cell agglutination test, the prevalence (Bywaters *et al.*, 1958; Kellgren and Ball, 1959) varying from 13 to 40% at the first test. This may be simply an age effect or may mean that other aetiological factors play a part. In a single kindred of 3,000 persons in which rheumatoid arthritis, spondylitis and Still's disease occurred, Whittinghill *et al.* (1958) found that the 5 patients with Still's disease had, as close relatives, persons with spondylitis rather than with juvenile or adult rheumatoid arthritis. Precise details of the criteria used for the diagnosis of Still's disease in this study are not available, but the position is complicated by the fact that a transient attack of polyarthritis precedes the onset of spinal symptoms in some 25% of patients with spondylitis and that there may be a considerable interval between the polyarthritic and the spondylitic phase (Hollister and Engleman, 1958).

A number of other diseases are associated with a positive sheep-cell agglutination test. These include disseminate lupus erythematosus, systemic sclerosis, polyarteritis nodosa and digital arteritis. Though convincing evidence of the effects of heredity is lacking, it is likely that the genes concerned with the rheumatoid serum factor are also influential in this group, possibly in combination with other genes. In disseminate lupus erythematosus, for example, the occurrence of hypergammaglobulinæmia in other members of the family has been recorded by Leonhardt (1957).

Osteoarthrosis

Heredity might be expected to influence osteoarthrosis in two ways: (1) By producing anatomical abnormalities of a certain joint, e.g. the hip which results in a mechanical predisposition. (2) By a metabolic change resulting in the formation of a less resilient type of articular cartilage.

In the first group may be included congenital dislocation of the hip in which both genetic and environmental factors are known to play a part (Carter, 1957) and multiple epiphyseal dysplasia which is thought to be inherited as a dominant and in which the hips and knees are mainly affected by osteoarthrosis (Barrie *et al.*, 1958). Familial coxarthrosis in three generations of a family has been described by Böni (1959). In two members of the fourth generation, trough-shaped defects were noted in the femoral heads. A rather similar family has been reported by Zinsli (1946).

There is also evidence that Perthe's disease, a not uncommon precursor of osteoarthrosis of the hip, has a genetic basis (Goff, 1954) and also slipped epiphysis (Ruther, 1954).

Generalized osteoarthrosis is encountered in two diseases already known to be genetically determined, gout and alkaptonuria, but neither of these offers any explanation for the majority of cases of generalized osteoarthrosis. That heredity may play a part in causation is suggested by the large proportion of those with generalized osteoarthrosis who have Heberden's nodes (Kellgren and Lawrence, 1958). These nodes have been shown by Stecher (1955*a*, *b*) to be inherited as a single autosomal gene which is dominant in females and possibly recessive in males.

In a familial study of generalized osteoarthrosis in Leigh and Wensleydale, radiological

appearances of osteoarthrosis in 4 or more types of joint were noted in 20 (24%) of male relatives but in only 10% of males in the general population. Of the female relatives, 31 (32%) had osteoarthrosis in 4 or more joints, but only 15% of the general population of females. This could not be accounted for by differences in age distribution nor could occupation, though often "inherited", have been responsible as the occupational distribution was similar to that in the general population. It is clear, therefore, that there is a high familial incidence of the generalized forms of osteoarthrosis.

Of 23 spouses who were examined, 21 were in the 55–64 age group and all those with osteoarthrosis in 4 or more joints were in this age group. The proportion at this age was 33% which may be compared with 21% and 31% respectively in males and females in the population sample and 45% and 50% in the relatives in this age group. It may be concluded that the familial aggregation of multiple osteoarthrosis is in all probability genetically determined.

In view of the many possible causative factors in osteoarthrosis, it must be considered whether more than one gene is commonly involved. When the relatives were divided up according to the presence or absence of Heberden's nodes in the propositi, it was found that in the nodal families 25% of females had moderate or severe Heberden's nodes, whereas in the non-nodal families, only 7% had nodes. In a matched sample from the general population, there were 8% with Heberden's nodes. None of these differences could be accounted for by age distribution. Male relatives in the nodal families did not have more nodes than the controls. Thus the inheritance of Heberden's nodes was confirmed in the females but not in the males. This is in conformance with Stecher's findings in which the male inheritance was less definite.

When osteoarthrosis in the nodal and non-nodal families was compared, the findings were quite different. Both in males and females there was just as much multiple osteoarthrosis in the non-nodal as in the nodal families. Indeed, the non-nodal families had rather more, but both had significantly more than the controls.

It would thus appear that, as in rheumatoid arthritis, more than one gene is commonly involved in the inheritance of multiple osteoarthrosis. In view of the predominance in the female sex, it may be considered whether one allele is shared with rheumatoid arthritis.

An examination of the prevalence of rheumatoid arthritis in the nodal and non-nodal families and the controls indicated that this might be so. Clinical inflammatory polyarthritis was encountered in 9% of relatives but in only 4% of controls. The difference was even more striking when nodal and non-nodal families were considered separately, 14% of the non-nodal relatives having clinical polyarthritis, 22% if only the females are considered. This difference is significant at the 1% level.

If one gene is shared between rheumatoid arthritis and generalized osteoarthrosis, it is important to discover whether it is one of those concerned with the sheep-cell agglutination test. In fact only 5% of relatives had a positive sheep-cell agglutination test compared with 6% of controls. It is thus not the alleles associated with rheumatoid serum factor which are shared between the rheumatoid arthritis and osteoarthrosis families. This is confirmed by findings in the survey of rheumatoid families (Lawrence and Ball, 1958). More multiple osteoarthrosis was found in the relatives of those with clinical rheumatoid arthritis than in the controls, but not in the relatives of those with a positive sheep-cell agglutination test only.

Rheumatic Fever

A high familial incidence of rheumatic fever has been reported in a number of family studies (Draper, 1926; Fraser-Roberts and Thomson, 1934; Irvine-Jones, 1933; Stevenson and Cheeseman, 1952). There has, however, been some uncertainty as to whether this is due to heredity or to the spread of infection in families. Lawrence (1922) found nearly the same prevalence in the families of rheumatic and tuberculous subjects in whom the opportunity for the spread of infection might be thought to be similar. However, Wilson (1940) and Broccoliche-Foullet (1954) found that in families in which both parents had had rheumatic fever, there was a greater incidence (94%) in siblings, than in families with one affected parent (55% of siblings affected) or in families with no parents affected (43% of siblings affected). This is strongly suggestive of a recessive inheritance. Moreover, Rammelkamp *et al.* (1952) found that of patients with proven streptococcal infection, only 3% develop rheumatic fever, suggesting that the constitutional factor is of major importance. Confirmation of the hereditary hypothesis has recently come from work on blood groups and group O secretor status in rheumatic fever subjects (Clarke *et al.*, 1960).

Gout

One of the first family studies to be made on a disorder involving connective tissue was by

Scudamore (1823) who described an investigation in which detailed family histories were taken of patients with gout. These indicated a hereditary factor which was confirmed in 1938 by Talbott and Coombs who examined families of gouty patients and estimated the serum uric acid. Stecher *et al.* (1949) from a survey of 201 relatives of gouty patients concluded that hyperuricæmia is an autosomal dominant with 84% penetrance in the heterozygous male and 12% in the female. This may well be the case but since serum uric acid in population samples is a continuous variable, giving a normal curve with a peak at 4 mg%, it is unlikely that a single autosomal dominant could be responsible and more probable that several autosomal dominant genes are involved.

Spondylitis

There is also some evidence of a genetic factor in spondylitis. Ray (1932) recorded the disease in twin brothers. Stecher and Hauser (1946) described 2 brothers suffering from the disease and cited 3 other instances in which more than 1 brother was affected. Other instances of the disease occurring in families have been reported by Campbell (1947), Rogoff and Freyberg (1949), West (1949), Mason (1950) and Tegner and Lloyd (1949).

Hersh *et al.* (1957) have compared 281 first degree relatives of spondylitics with 3,335 relatives of controls. Seven (2·5%) of the spondylitics' relatives had spondylitis, compared with 6 (0·2%) of controls. Stecher, from an analysis of these families, concluded that the condition is definitely inherited but not as a sex-linked character. He considers the condition an autosomal dominant and that the sex difference which exists is due to a higher penetrance in men.

Other Diseases

Evidence of a genetic factor has been observed in a number of other connective tissue disorders, particularly in diseases of bone such as Paget's disease (Roberts and Cohen, 1926; Brailsford, 1938; Gutman and Kasbach, 1936), achondroplasia, Morquio's disease (Brailsford, 1929; Morquio, 1929), pleonosteosis and osteopoikilosis, cleidocranial dysostosis and Albers-Schönberg disease. For details of these and many other heritable connective tissue disorders, McKusick's (1956) very comprehensive review should be consulted. Of the arthropathies not so far considered, psoriatic arthropathy is likely to have a genetic basis in view of the known importance of heredity in the skin lesions. A rare form of arthritis which may be familial is lipoid dermatoarthritis in which the joint condition is associated with a papular and nodular eruption (Warin *et al.*, 1957).

Conclusions

Heredity obviously plays an important part in disorders of connective tissue. This should not, however, make us despondent about their eventual control. Environmental factors are also important particularly in the more common diseases and may point the way to prevention. It may even be possible to control the genetic factors. It is probable that most if not all genetically determined diseases are due basically to metabolic defects which, if fully understood, could be controlled as in the case of phenylketonuria. Some such method may be the eventual answer to the successful control of rheumatoid arthritis and generalised osteoarthrosis.

REFERENCES

Barrie, H., Carter, C., and Sutcliffe, J. (1958) *Brit. med. J.*, ii, 133.

Böni, A. (1959) *Seminar int.*, **8**, 16.

Brailsford, J. F. (1929) *Amer. J. Surg.*, **7**, 404.

——— (1938) *Brit. J. Radiol.*, **11**, 507.

Bremner, J. M., Alexander, W. R. M., and Duthie, J. J. R. (1959) *Ann. Rheum. Dis.*, **18**, 279.

Broccoliche-Foulet, J. (1954). A propos du caractère familial de la maladie de Bouillaud, Thesis, Paris.

Bywaters, E. G. L., Carter, M., and Scott, F. J. (1958) *Lancet*, ii, 1316.

Campbell, A. M. G. (1947) *Lancet*, i, 406.

Carter, C. (1957) *Lancet*, ii, 986.

Clarke, C. A., McConnell, R. B., and Sheppard, P. M. (1960) *Brit. med. J.*, i, 21.

Draper, G. (1926) *Amer. J. med. Sci.*, **171**, 803.

Fraser-Roberts, J. A., and Thomson, W. A. R. (1934) *Ann. Eugen., Lond.*, **6**, 3.

Goff, C. W. (1954) Legg-Calvé-Perthe's Syndrome. Springfield, Ill.

Gutman, A. B., and Kasbach, H. (1936) *Amer. J. med. Sci.*, **191**, 361.

Hersh, A. H., *et al.* (1957) quoted by Stecher, R. M. (1957) *Docum. rheum. Geigy*, **12**, 42.

Hollister, L. E., and Engleman, E. P. (1958) *J. chronic Dis.*, **8**, 334.

Irvine-Jones, E. (1933) *Amer. J. Dis. Child.*, **45**, 1184.

Kellgren, J. H., and Ball, J. (1959) *Brit. med. J.*, i, 523.

———, and Lawrence, J. S. (1956) *Ann. Rheum. Dis.*, **15**, 1.

———, ——— (1958) *Ann. Rheum. Dis.*, **17**, 388.

Lawrence, W. S. (1922) *J. Amer. med. Ass.*, **79**, 2051.

———, and Ball, J. (1958) *Ann. Rheum. Dis.*, **17**, 160.

Leonhardt, T. (1957) *Lancet*, ii, 1200.

Lewis-Faning, E. (1950) *Ann. Rheum. Dis.*, **9**, Suppl.

McKusick, V. A. (1956) Heritable Disorders of Connective Tissue. St. Louis.

MASON, R. M. (1950) *Rep. W. Lond. Hosp., Dept. rheum Dis.*, p. 17.
MIALL, W. E. (1955) *Ann. Rheum. Dis.*, **14,** 150.
MORQUIO, L. (1929) *Bull. soc. Pédiat. Paris*, **27,** 145.
NERI SERNERI, G. G. and BARTOLI, V. (1956) *Acta genet. med. gemel.*, **5,** 502.
RAMMELKAMP, C. H., WANNAMAKER, L. W., and DENNY, F. W. (1952) *Bull. N.Y. Acad. Med.*, **28,** 321.
RAY, M. B. (1932) *Proc. R. Soc. Med.*, **25,** 325.
ROBERTS, R. E., and COHEN, M. J. (1926) *Proc. R. Soc. Med.*, **19,** Sect. Electrother. p. 13.
ROGOFF, B., and FREYBERG, R. H. (1949) *Ann. Rheum. Dis.*, **8,** 139.
RUTHER, H. (1954) Ursachen u. Behandlung der Jugendlichen Hüftkopflösung. Stuttgart.
SCUDAMORE, C. (1823). A Treatise on the Nature and Cure of Gravel. 4th ed. London.
SHORT, C. L., ABRAMS, N. R., and SARTWELL, P. E. (1952). Proceedings of the VII International Congress of Rheumatic Diseases. Philadelphia; p. 47.
STECHER, R. M. (1953) *Amer. J. Hum. Genet.*, **5,** 118.
—— (1955*a*) *Ann. Rheum. Dis.*, **14,** 1.
—— (1955*b*) *Med. Clin. N. Amer.*, **39,** 499.
——, and HAUSER, H. (1946) *Amer. J. Roentgenol.*, **56,** 601.
STECHER, R. M., HERSH, G. H., and SOLOMON, W. M. (1949) *Ann. intern. Med.*, **31,** 595.
——, SOLOMON, W. M., and WOLPAW, R. (1952) Proceedings of the VII International Congress of Rheumatic Diseases. Philadelphia; p. 66.
STEVENSON, A. C., and CHEESEMAN, E. A. (1952) *Ann. Eugen. Lond.*, **17,** 177.
TALBOTT, J. H., and COOMBS, F. S. (1938) *J. Amer. med. Ass.*, **110,** 1977.
TEGNER, W., and LLOYD, K. (1949) *Lancet*, ii, 196.
VALKENBERG, H. A., and BALL, J. (1960) Personal communication.
WARIN, R. P., EVANS, C. D., and HEWITT, M. (1957) *Brit. med. J.*, i, 1387.
WEST, H. F. (1949) *Ann. Rheum. Dis.*, **8,** 143.
WHITTINGHILL, M., HENDRICKS, E. E., TAYLOR, G. S., and THORP, L. S. (1958) Proceedings of the X International Congress of Genetics. Toronto; **2,** 314.
WILSON, M. G. (1940) Rheumatic Fever Studies of the Epidemiology, Manifestations, Diagnosis and Treatment of the Disease During the First Three Decades. London.
ZINSLI, P. E. (1946) Arthrosis deformans der Hüfteals Erbleiden (Epiphysen-Deformation). Thesis. Zurich.

Meeting
May 21, 1960

MEETING AT ST. RICHARD'S HOSPITAL, CHICHESTER

THE following papers were read:

Discussion on Surgical Procedures for Osteoarthritis of the Hips.—Mr. J. R. ADDISON.

The Effect of Stretch on Spastic Muscle.—Dr. JOHN FOLEY.

Pain and Stiffness in the Pelvis and Shoulders of a Non-specific Nature.—Dr. DONALD WILSON.

The Use of Fibre Glass in Medicine.—Flight Lieutenant KNIGHT.

The following cases were shown:

Systemic Lupus Erythematosus.

Amyloidosus.

Flaccid Paresis.

Atypical Syringomyelia.

Sarcoidosis.

Meeting
June 8, 1960

DR. BASIL KIERNANDER delivered his Presidential Address entitled **The World Development of the Cheshire Homes for the Disabled.** The Address will appear in *The Cheshire Smile*, September 1960.

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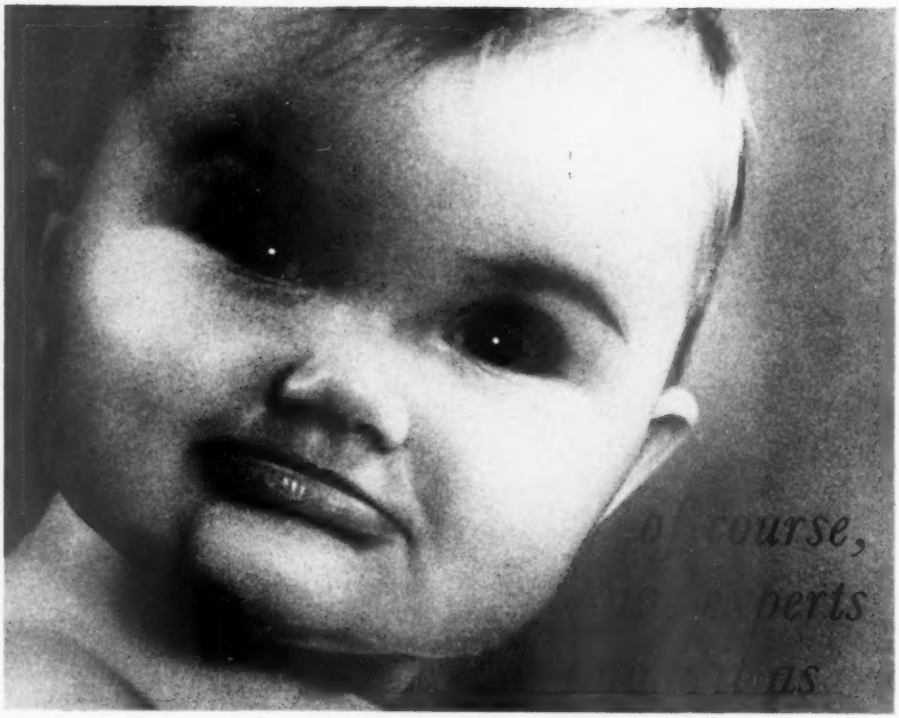

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Section of Odontology

President—F. C. Wilkinson, C.B.E., M.D., F.R.C.S., F.D.S.

Meeting
March 28, 1960

A Hair Follicle in Human Cheek Mucosa

By Professor A. E. W. Miles, F.D.S., L.R.C.P., M.R.C.S.
London

The occurrence of a hair follicle in human cheek mucosa does not appear to have been hitherto described. During the course of the examination of 180 specimens of cheek mucosa from autopsies in connexion with a study of the buccal sebaceous glands (Miles, 1958*a*), a single hair about 0·5 cm long was observed projecting from the mucosa of a male aged 57 years. The hair was situated about 0·5 cm behind and at the level of the parotid papilla. With a stereoscopic dissecting microscope the hair was seen to be emerging from a small opening from which a bead of sebum was also projecting (Fig. 1). A large group of sebaceous glands was related to the base of the hair. The mucosa contained many other sebaceous glands but no other hairs could be found.

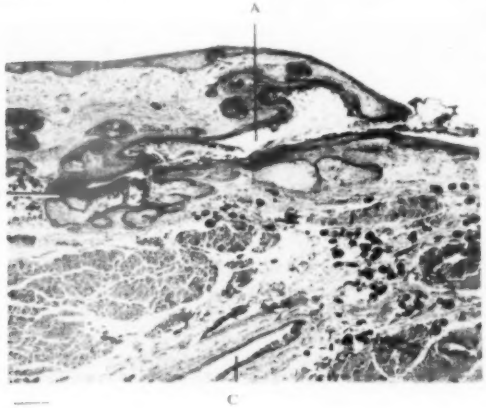
Serial sections through the region containing the hair showed that it arose from a typical active hair follicle (Figs. 2 and 3).

No explanation can be offered of the unusual finding reported here but a number of considerations are worthy of comment.

The site of fusion between the maxillary and mandibular processes during embryonic life is a line passing backwards from the angle of the mouth more or less parallel with the occlusal plane of the teeth at rest. The situation of the hair follicle a short distance behind the parotid papilla is too far above this line of fusion for it to be likely that the hair follicle developed from skin ectoderm included as part of the oral mucosa during the process of embryonic "fusion."

The finding calls to mind that in some mammals, for example the Rodentia, the inner aspect of the cheek is lined partially with hairy skin. This condition appears to be a specialization associated with division of the mouth into gnawing and masticatory compartments, and no

Fig. 1.—A hair, associated with a bead of sebum, projecting from an opening in the surface of the mucosa. × 15.



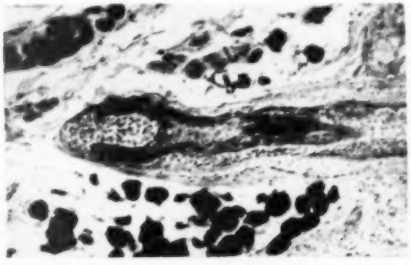


Fig. 3.—Higher power view of the hair bulb. Stained hæmatoxylin and eosin. × 82.

←Fig. 2.—Longitudinal section through hair shaft, A, containing sebum and a few scraps of the hair which fragmented during sectioning. B, the hair bulb associated with many sebaceous lobules. C, the parotid duct. Stained hæmatoxylin and eosin after treatment in bulk with Flemming's solution. × 22.

evidence has ever been adduced that hairiness of the inner aspect of the cheek is a condition that existed in the remote ancestors of man. The occurrence of a single hair follicle in a human cheek mucosa is unlikely therefore to have any phylogenetic significance.

On *a priori* grounds it would seem probable that this hair follicle arose as an aberration of development during fœtal or early life. It has been shown, however, that even during late adult life sebaceous glands develop in human oral mucosa previously devoid of them (Miles, 1958*a*, *b*). The possibility cannot be discounted therefore that this hair follicle also developed relatively late in life.

REFERENCES

MILES, A. E. W. (1958*a*) *Brit. dent. J.*, **105**, 235.
—— (1958*b*) *J. dent. Res.*, **37**, 757.

Experimental Dental Caries in the Rat

By R. L. HARTLES, D.Sc., Ph.D.

Liverpool

To obtain detailed information concerning the effect of various factors upon the initiation and development of dental caries it is necessary to have available an experimental animal in which can be produced an adequate and acceptable version of human dental decay. The Rhesus monkey has a tooth form approximating reasonably closely to that of man, and it develops caries within nne to three years, but it is a comparatively large animal and its use in studies requiring many individuals is rarely feasible. The albino rat which has been used so successfully in a large number of biological investigations is the animal of choice in the study of experimental caries.

Occurrence of dental caries in the rat.—When maintained on natural diets the rat does not normally develop caries. Some strains of rat are highly resistant to the onset of the disease in any dietary circumstances, and it is apparent that genetic factors play an important part in caries susceptibility in the rat (Hunt *et al.*, 1955). Nevertheless certain strains of caries-susceptible animals have been bred and are available for the study of the disease.

Type of dentition in the rat.—The rat has an incisor and three molars in each quadrant of the jaw. The incisor is continuously erupting and is not suitable for studying caries. The three molars together measure about 7 mm mesiodistally and the average width is about 2 mm.

FIG. 1.—Second right mandibular molar of rat. The lingual surface has been ground away and the exposed dentine stained with alizarin red-S. Note the depth of the buccolingual fissures.

The molars are traversed by several deep buccolingual fissures and the tips of the cusps are developmentally devoid of enamel. Fig. 1 shows a second mandibular molar which has been ground lingually to show the depth of the fissures. It is stained with alizarin red-S to differentiate the enamel and dentine.

Site of caries.—In our own animals only fissure caries has been observed and this is the type of the disease which will be discussed. Other workers (Stephan, 1951; McClure, 1952) have described the production of interproximal and smooth surface lesions in the rat. This subject has been well reviewed by Stephan and Harris (1955). Fig. 2 illustrates the appearance of gross fissure caries in the first mandibular molar. Fig. 3 shows occlusal views of gross fissure caries. It is widely accepted that the rat develops various degrees of tooth decay which are similar in many respects, both microscopically and grossly, to caries in man.

Dietary regime necessary for the production of dental caries.—One of the earliest cariogenic diets to be studied systematically was that designed by Hoppert *et al.* (1932). This was a diet containing coarse corn particles; if the diet was finely ground so that it all passed through a sixty-mesh sieve no caries was produced. It was considered that the impaction of the hard particles of the diet within the fissures of the molar teeth was a significant factor in the production of this kind of caries. Whilst much valuable information was obtained, it was an unsatisfactory type of the disease if comparison were to be made with tooth decay in man.

Subsequently, McClure (1945), Sognnaes (1948) and Shaw (1950) described carious lesions in rats which had received finely powdered purified diets containing 67% of sucrose and nutritionally adequate for the rat. It is now accepted that impaction of food and subsequent fracture play little part in the initiation of this type of rat caries. Other workers have used similar

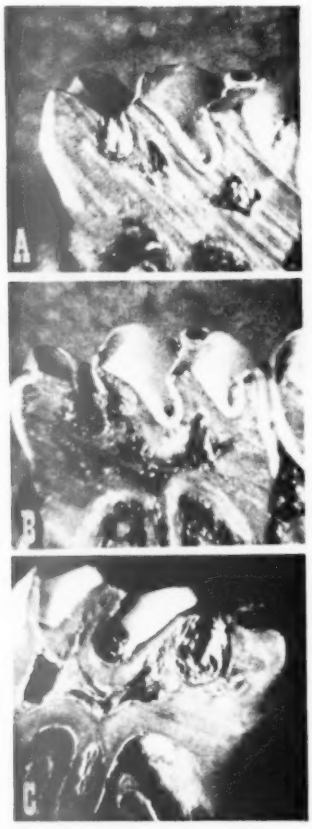


FIG. 2.—First right mandibular molar (A and B) and first left mandibular molar (C), ground and stained as in Fig. 1 to show carious lesions at different stages of development.

purified diets (Hartles *et al.*, 1956), the major components of which are given in Table I. On

TABLE I.—COMPOSITION OF THE HIGH-SUGAR DIET (HS 1) WITHOUT SUPPLEMENTS*

	g/kg
Sucrose	670
Casein, soluble	200
Hepamino	40
Groundnut oil	50
Salt mixture	40

*Adapted from Hartles *et al.* (1956).

this type of diet gross caries develops in three to six months, mainly in the mandibular molars. If the sugar in the diet is replaced by potato starch the incidence of caries is very much reduced (Hartles and Lawton, 1957), *see* Table II. The figures quoted in Table II also give an indication of the difference in distribution of the lesions between the mandibular and maxillary molars. This observation has been confirmed

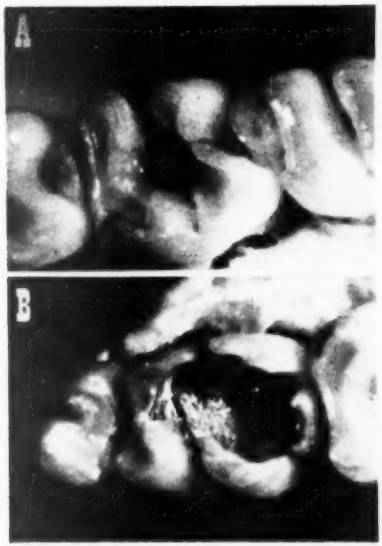


FIG. 3.—Occlusal view of carious lesions in (A) second and (B) first mandibular molars of the rat.

by many workers. It is, however, unjustifiable to claim that the maxillary molars *per se* are less susceptible to decay than the mandibular molars, since variation in local environmental factors may be a major cause of the difference.

TABLE II.—DEVELOPMENT OF DENTAL CARIES IN RATS MAINTAINED ON DIETS CONTAINING 67% SUCROSE (GROUP 1) OR 67% POTATO STARCH (GROUP 2)*

	No. of rats	Age at death (weeks)	No. of rats with caries	No. of carious teeth	No. of carious teeth per rat
Group 1					
Males	20	26	17	43	2·15
Females	20	26	13	29	1·45
Total	40		30	72	1·80
Group 2					
Males	19	26	5	10	0·53
Females	19	26	6	9	0·47
Total	38		11	19	0·50

*Adapted from Hartles and Lawton (1957).

Influence of pre-natal diet upon the development of caries in the rat.—It is important to distinguish between the local effect of a particular dietary regime and the truly nutritional effect operating throughout the period of tooth development. The early work of Sognnaes (1948) showed that the greatest incidence of caries was in those rats which had been exposed to the influence of the cariogenic diet during their ante-natal, suckling and post-weaning life. A summary of Sognnaes' results is shown in Table III.

The purified diet used, whilst adequate for

TABLE III.—COMPARISON OF CARIES SUSCEPTIBILITY IN HAMSTERS, RATS, AND MICE "BRED" ON STOCK DIET AND ON A PURIFIED DIET*

Species	No. of animals	Diet in pregnancy and lactation	Posteruptive experimental period: Diet	Posteruptive experimental period: Length (months)	Mean caries incidence No. of molars affected
Hamster	6	Stock	Purified	4	4·6
Rat ..	12	Stock	Purified	4	0
Mouse ..	15	Stock	Purified	4	0
Hamster	3	Purified	Purified	2	9·0
Rat ..	10	Purified	Purified	2	2·4
Mouse ..	21	Purified	Purified	2	0·4

*Adapted from Sognnaes (1948).

TABLE IV.—OVERALL RESPONSE OF NORMAL AND DESALIVATED RATS TO PURIFIED RATION (BASIC) AND ASH-SUPPLEMENTED PURIFIED RATION (ASH)*

Condition of animals	No. of rats	Dietary History: Pregnancy and lactation	Dietary History: Postweaning	Average no of carious lesions
Normal ..	47	Basic	Basic	6·2
	50	Ash	Basic	4·2
	13	Ash	Ash	1·4
Desalivated	45	Basic	Basic	21·0
	61	Ash	Basic	23·2
	23	Ash	Ash	21·2

*Adapted from Sognnaes and Shaw (1954).

growth and reproduction of the rat, does not guarantee the development of caries-resistant teeth. A "natural" diet on the other hand does seem to produce a greater degree of resistance to caries. The question is, how much does this effect owe to local environmental factors operating post-eruptively, and how far is it caused by truly nutritional factors operating during the period of tooth development? It is not easy completely to separate these two factors. In the rat first molar the enamel begins to calcify at birth, appositional growth is completed at about the tenth to eleventh day, and the tooth starts to erupt at the nineteenth day. The second molar is two or three days later in its development, and the third molar does not begin to calcify until fifteen days after birth and first appears in the oral cavity at the thirty-fifth day.

The first attempts to determine the "protective" factors in natural diets were directed towards the mineral content (Sognnaes and Shaw, 1954). The natural diet, a laboratory pelleted food, was ashed at 550 C; the resulting ash was then used as the sole source of minerals in the purified diet in place of the salt mixture normally added to the diet. When this modified diet was given to rats during pregnancy and lactation, and the offspring weaned on to the original purified diet, there was a significant reduction in the incidence of dental caries. When the modified diet was given throughout the pre- and post-natal life there was an even greater reduction in caries (Table IV). One interpretation of these results is that the "natural" ash influences the development of caries in the rat both developmentally and environmentally. The authors showed that the effect was not caused by the fluoride content of the ash. This is a potentially profitable line of investigation and may eventually reveal trace elements other than fluoride which are essential for the development of a caries-resistant enamel. In this respect it is interesting to note the unconfirmed observations of Adler (1957) who reported that drinking water containing 0·1 ppm of molybdenum reduced the incidence of caries in albino rats. It should, however, be pointed out that the animals used in this experiment were receiving a diet of coarsely ground maize meal, a regime producing the "fracture" type of rat caries.

The influence of the oral environment upon the development of dental caries in the rat.—There are two major factors which bear on the production of dental caries: (1) The inherent resistance of the tooth which, as already discussed, may be influenced by nutritional factors. (2) The effect of the tooth's environment.

The environmental effect can be studied under three main headings: (*a*) The influence of oral micro-organisms. (*b*) The effect of suitable substrates on the metabolism of the micro-organisms. (*c*) The influence of the salivary secretions.

The presence of micro-organisms—germ-free animals.—One of the most important contributions which has been made in the study of rat caries has been the demonstration that the disease does not develop in animals which have been born and bred in a germ-free environment (Orland, 1955). These germ-free animals did not develop caries when given a diet which was highly cariogenic when fed to similar but non-sterile animals.

The necessity for the presence of suitable substrates in the mouth for the production of caries in the rat.—The importance of the presence of suitable substrates in the oral environment has been beautifully demonstrated in the rat by Kite *et al.* (1950). They administered cariogenic diets to one group of animals in the normal manner and to another group by stomach tube. In addition a number of animals in each group was desalivated, a procedure known to increase the caries experience of the individual animal. The results are shown in Table V. In the intact animals, those receiving diet in the normal way developed caries, those fed by stomach tube did not. In the desalivated animals the caries experience of the normally fed animals was greatly increased; there was still no caries in the tube-fed animals. As a result of these experiments two most important factors, which were long suspected, have been conclusively demonstrated as being of importance in the production of dental

TABLE V.—INCIDENCE OF CARIES IN RATS FED BY STOMACH TUBE*

Condition	Method of feeding	No. of rats	Average per rat: Numbers of carious molars	Carious lesions	Caries score
Intact ..	Normal	13	5·0	6·7	10·6
	Stomach tube	13	0	0	0
Desalivated	Normal	4	11·5	28·8	124·8
	Stomach tube	3	0	0	0

*Adapted from Kite *et al.* (1950).

caries in the rat: (1) In the complete absence of micro-organisms but in the presence of food debris, caries does not develop. (2) In the complete absence of food debris but in the presence of abundant micro-organisms caries again does not develop. Further, it has been shown that caries-susceptible animals maintained on a diet rich in protein and fat but essentially devoid of carbohydrate do not develop caries.

The influence of the salivary secretions.—The removal of the salivary glands, particularly the parotid, causes a great increase in the caries experience of the rat (Tables IV and V). This subject has been reviewed by Schwartz and Weisberger (1955). The earlier in life that the glands are removed, the greater is the effect on the development of caries. This has led to the suggestion that the saliva has a part to play in the maturation of the rat enamel. This lacks conclusive experimental proof although it has been shown that the ability of rat enamel to take up stain and radioisotopes diminishes with increasing age.

It has also been postulated that changes in the salivary gland secretions may explain the altered caries-susceptibility observed following interference with the function of certain endocrine glands. Hypophysectomy in the rat leads to histological changes in the submaxillary glands and to an increase in dental caries (Shafer and Muhler, 1955). Bixler *et al.* (1955) observed changes in the adrenals after removal of the salivary glands from the rat. It has also been reported that the injection of œstrogens into intact rats caused a greater increase in caries than did the injection of androgens (Muhler and Shafer, 1955). Several observers during the last few decades have claimed that human sufferers from diabetes mellitus are especially prone to dental decay. Nichols and Shaw (1957) could not demonstrate any increase in caries in rats rendered diabetic by intravenous injection of alloxan. Other workers, however, have reported an increase in caries experience in the rat following the injection of alloxan (Hartles and Lawton, 1958) (Table VI).

A possible interrelationship between the endocrine system and salivary secretions is potentially of the utmost importance. If the balance of the oral environment can be altered by endocrine imbalance, it may go far to explain many of the apparent anomalies so frequently observed in the caries experience of individual humans.

TABLE VI.—DISTRIBUTION AND SEVERITY OF CARIES IN THE MANDIBULAR AND MAXILLARY MOLARS OF RATS INJECTED WITH ALLOXAN MONOHYDRATE AND OF CONTROL RATS*

	Percentage of molars with caries: Group 1 (injected)	Group 2 (controls)	Percentage of molars with scores of 2 and 3: Group 1 (injected)	Group 2 (controls)
Males:				
Mandible	66	40	40	22
Maxilla	26	6	16	3
Total	46	23	28	12
Females:				
Mandible	47	27	26	15
Maxilla	13	2	10	1
Total	30	14	18	8
Males and Females:				
Mandible	58	34	34	19
Maxilla	21	4	13	2
Total	39	19	24	10

*Taken from Hartles and Lawton (1958).

In this brief survey an attempt has been made to show that the rat is an animal in which an acceptable version of human dental caries can be produced. The occurrence of the disease in the rat offers the possibility of studying the factors involved in the ætiology of caries in a controlled fashion, and by its intelligent use it may enable information to be gathered which would be difficult to obtain if studies were confined to man.

REFERENCES

ADLER, P. (1957) *Odont. Revy*, **8,** 202.
BIXLER, D., MUHLER, J. C., and SHAFER, W. G. (1955) *J. dent. Res.*, **34,** 889.
HARTLES, R. L., and LAWTON, F. E. (1957) *Brit. J. Nutr.*, **11,** 13.
——, —— (1958) *Brit. J. Nutr.*, **12,** 286.
——, ——, and SLACK, G. L. (1956) *Brit. J. Nutr.*, **10,** 234.
HOPPERT, C. A., WEBBER, P. A., and CANNIFF, T. L. (1932) *J. dent. Res.*, **12,** 161.
HUNT, H. R., HOPPERT, C. A., and ROSEN, S. (1955) In: Sognnaes (1955) p. 66.
KITE, O. W., SHAW, J. H., and SOGNNAES, R. F. (1950) *J. Nutr.*, **42,** 89.
MCCLURE, F. J. (1945) *J. dent. Res.*, **24,** 239.
—— (1952) *Science*, **116,** 229.
MUHLER, J. C., and SHAFER, W. G. (1955) *J. dent. Res.*, **34,** 661.
NICHOLS, M. S., and SHAW, J. H. (1957) *J. dent. Res.*, **36,** 68.
ORLAND, F. J. (1955) In: Sognnaes (1955) p. 169.
SCHWARTZ, A., and WEISBERGER, D. (1955) In: Sognnaes (1955) p. 125.
SHAFER, W. G., and MUHLER, J. C. (1955) *J. dent. Res.*, **34,** 531.
SHAW, J. H. (1950) *J. Nutr.*, **41,** 13.
SOGNNAES, R. F. (1948) *J. Amer. dent. Ass.*, **37,** 676.
——, ed. (1955) Advances in Experimental Caries Research. Washington.
——, and SHAW, J. H. (1954) *J. Nutr.*, **53,** 195.
STEPHAN, R. M. (1951) *J. dent. Res.*, **30,** 484.
——, and HARRIS, M. R. (1955) In: Sognnaes (1955) p. 47.

BOOKS RECEIVED FOR REVIEW

Adams (A. R. D.), and **Maegraith (B. G.).** Clinical tropical diseases. 2nd ed. pp. x+540. Oxford: Blackwell. 52s. 6d. 1960.

Ballantine (R. I. W.), and **Jackson (I.).** A practice of general anæsthesia for neurosurgery. pp. viii+152. London: Churchill. 27s. 6d. 1960.

Bonin (G. Von). Some papers on the cerebral cortex. Translated from the French and German. American Lecture Series No. 332. pp. xxiv+396. Springfield, Ill.: Thomas. Oxford: Blackwell. 92s. 1960.

Bowers (W. F.). Interpersonal relationships in the hospital. pp. vii+125. Springfield, Ill.: Thomas. Oxford: Blackwell. 40s. 1960.

Bowers (W. F.). Surgical gastroenterology. pp. xii+498. Springfield, Ill.: Thomas. Oxford: Blackwell. £7 8s. 1960.

Bowers (W. F.), and **Hughes (C. W.).** Surgical philosophy in mass casualty management. pp. ix+204. Springfield, Ill.: Thomas. Oxford: Blackwell. 54s. 1960.

Bowesman (C.). Surgery and clinical pathology in the tropics. pp. viii+1067. Edinburgh and London: Livingstone. £5 10s. 1960.

Butt (A. J.), ed. Treatment of urinary lithiasis. pp. xxii+577. Springfield, Ill.: Thomas. Oxford: Blackwell. £8 8s. 1960.

Caraway (W. T.). Microchemical methods for blood analysis. pp. xi+109. Springfield, Ill.: Thomas. Oxford: Blackwell. 42s. 1960.

Catzel (P.). The pædiatric prescriber. pp. xvi+244. Oxford: Blackwell. 15s. 1959.

Conn (H. F.), ed. Current therapy—1960. Latest approved methods of treatment for the practising physician. pp. xxxii+808. Philadelphia and London: Saunders. 84s. 1960.

Cosentino (R.). Atlas of anatomy and surgical approaches in orthopædic surgery—upper extremity. pp. xiv+192. Springfield, Ill.: Thomas. Oxford: Blackwell. 84s. 1960.

Cross (L. M.). The preparation of medical literature. pp. xx+451. London: Pitman. 80s. 1959.

Davidson (Sir S.), ed. The principles and practice of medicine. A textbook for students and doctors. 5th ed. pp. xi+1112. Edinburgh and London: Livingstone. 35s. 1960.

Dekaban (A.). Neurology of infancy. pp. xiv+388. Baltimore: Williams and Wilkins. London: Baillière. 96s. 1959.

Delaney (J. W.). Handbook of hæmatological and blood transfusion technique. pp. x+311. London: Butterworth. 45s. 1960.

DeMartino (M. F.), ed. Dreams and personality dynamics. pp. xvii+377. Springfield, Ill.: Thomas. Oxford: Blackwell. 84s. 1959.

Denber (H. C. B.), ed. Research conference on therapeutic community. pp. xvi+265. Springfield, Ill.: Thomas. Oxford: Blackwell. 88s. 1960.

Discombe (G.). Blood transfusion. A guide to the practice of transfusion within hospitals. 2nd ed. pp. iv+58. London: Heinemann. 6s. 1960.

Durham (R. H.). Encyclopedia of medical syndromes. pp. xiv+628. New York: Hoeber. London: Pitman. £5 10s. 1960.

Forsyth (G.), and **Logan (R. F. L.).** The demand for medical care. A study of the case-load in the Barrow and Furness group of hospitals. pp. 153. London: Oxford University Press (for the Nuffield Provincial Hospitals Trust). 7s. 6d. 1960.

Gibson (H. L.). The photography of patients. 2nd ed. American Lecture Series No. 372. pp. ix+200. Springfield, Ill.: Thomas. Oxford: Blackwell. 84s. 1960.

Glassman (J. A.), and **McNealy (R. W.).** Care of the surgical patient. pp. 320. Baltimore: Williams and Wilkins. London: Baillière. 52s. 1959.

Grollman (A.). Pharmacology and therapeutics. A textbook for students and practitioners of medicine and its allied professions. 4th ed. pp. 1079. London: Kimpton. 93s. 6d. 1960.

Hanlon (J. J.). Principles of public health administration. 3rd ed. pp. 714. St. Louis: Mosby. London: Kimpton. 78s. 6d. 1960.

Hayhoe (F. G. J.). Leukæmia. Research and clinical practice. pp. viii+335. London: Churchill. 80s. 1960.

Illingworth (R. S.). The development of the infant and young child: Normal and abnormal. pp. viii+318. Edinburgh and London: Livingstone. 27s. 6d. 1960.

Jefferson (Sir G.). Selected papers. pp. xi+563. London: Pitman. £5 5s. 1960.

Lawson (J. H.), ed. A synopsis of fevers and their treatment. 10th ed. pp. viii+184. London: Lloyd-Luke. 10s. 1960.

Lewis (L. A.). Electrophoresis in physiology. 2nd ed. American Lecture Series No. 385. pp. v+120. Springfield, Ill.: Thomas. Oxford: Blackwell. 44s. 1960.

(Contd. on p. 550)

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Section of General Practice

President—R. J. F. H. PINSENT, M.D.

Meeting
January 20, 1960

DISCUSSION ON EARLY AMBULATION

Dr. Lawrence Dulake (General Practitioner, Reigate):

Healthy people resent illness, particularly if it necessitates complete confinement to bed. It implies a surrender of the will to others together with loss of normal privacy, and a state of imposed helplessness related to personal cleanliness, excretory functions, feeding, posture and sleep. It is strange, therefore, how complacently the medical and nursing professions have for a long time accepted the humiliating experience of confinement to bed as an often essential part of treatment.

Since the war, early ambulation has replaced prolonged confinement to bed as a positive part of treatment in numerous conditions.

It is common experience in general practice that domiciliary visits are now fewer and attendances at surgery more numerous. This is also evident in the domiciliary care of children. Though some children will struggle to remain ambulant when actually ill, more parents now accept the natural instinct of the child to get up and play as soon as the illness is abating. One of the neatest articles on early ambulation is that of Asher (1947) entitled "The Dangers of Going to Bed": "Look at the patient lying in bed. What a pathetic picture he makes! The blood clotting in his veins, the lime draining from his bones, the scybala stacking up in his colon, the flesh rotting from his seat, the urine leaking from his distended bladder, and the spirit evaporating from his soul."

The bad effects of staying in bed are numerous: atrophy of muscle, increased susceptibility to infection, urinary and bowel disturbances, thrombo-embolic disease, emotional disturbance, osteoporosis and disturbed nitrogen balance, while in the aged pulmonary stasis may administer the final blow. The bedpan is an appliance which is humiliating, unphysiological and causes more physical strain than use of the bedside commode. The psychological affront of defæcation in semi-public inhibits natural reflexes, and the earlier the patient can be taken to the privacy of a closet the better it is for mind and body.

In general practice the shortening of disease by modern therapy renders the patient ambulant throughout most severe acute infections. The helpless exhaustion of patients with pneumonia before antibiotics were discovered is no longer seen. As the range of illnesses which can be treated at home extends, demand for hospital beds will fall, and could fall faster if general practitioners were furnished with certain ancillary aids on an extended scale:

(1) X-ray and pathological laboratory facilities to expedite diagnosis and control therapy.

(2) A domiciliary consultant service designed to assist in retaining the patient at home, rather than admitting him to hospital for relatively simple investigations.

(3) More District Nurses.

(4) A better home help service, whereby the household can get the invalid out of bed. It is easier to leave the patient in bed if short-handed.

(5) A domiciliary physiotherapy service. This is of particular value in pulmonary disease, and in geriatric cases. Semi-paralytics can also be kept ambulant by this means.

That absolute recumbency puts a greater load on the heart than the sitting position was pointed out by January (1956) in an article on early versus late ambulation in the treatment of cardiac patients. Sitting in a chair involves 23% less work for the heart than recumbency. Though sitting is not ambulation, the ability to walk is not as long delayed as in the patient kept in bed. In myocardial infarction improved cardiography and assessment permit variations in the time during which ambulation must be forbidden. January suggests that chair rest on the second to fourth day after infarction, as soon as shock has subsided, the use of the commode, and anti-coagulant therapy will cause less strain to the damaged heart. Rupture of the heart is rare after three weeks, and ambulation may be safe in four to five weeks for patients with small infarcts. Brummer *et al.* (1956) suggested an average stay in bed of sixteen days. However, their series of 332 cases of myocardial infarction showed an increase of residual infarction within four weeks of discharge. This would suggest that such a programme is unsafe and that the rate of healing of the infarct cannot be accelerated.

Early ambulation has been applied particularly to surgical patients. Nearly every patient is made ambulant as soon as possible, large numbers

standing and walking within twelve hours of operation. By early use of the calf pump and the diaphragm with its pump-like action on the vena cava, the vicious circle of stagnation in the capillaries can be reversed (Leithauser and Saraf, 1953). Vital capacity can show a reduction of as much as 80% after major abdominal procedures, taking fourteen days to return to normal if the patient is kept in bed and only two to five days if the patient is ambulant. Before the war cases of uncomplicated appendicitis were kept in bed for fourteen days and most major surgical cases for three weeks. Surgeons at the time feared the "burst abdomen", and it was not till shortly before the last war that the absence of granulation and fibrous tissue formation was recognized as a clinical entity due to vitamin-C and certain amino-acid deficiencies.

One of the last of the common surgical procedures to be influenced by early ambulation is the repair of hernia. Palumbo and Paul in 1952 published a study of the effects of early ambulation in hernioplasty. They divided a series of 642 inguinal herniotomies, all operated on by a group of surgeons employing the same methods, into three groups: group 1 was ambulant in fourteen days, group 2 in seven days, and group 3 on the first day. There were sixty-three post-operative complications (9·8%), these being three times more common in group 1 than in group 3. Wound complications were not increased, the recurrence rate after two years was lower, and the early ambulation group represented a saving of 1,600 hospital days compared with the late ambulation group. In a large series of 2,955 patients who underwent a variety of major operations, 1,735 were ambulant within twenty-four hours, and 1,220 were ambulant later. The morbidity and complication rates were similar to those after hernioplasty, and the post-operative mortality was reduced.

Apart from the effect on the individual patient, early ambulation has had an impact on ward management and hospital design. Wards were originally designed to accommodate patients largely confined to bed. Ambulant patients were a small minority awaiting discharge within forty-eight hours. The whole routine of the ward revolved round this fact, and many of the tedious restrictions and rules of ward administration were, and still are, due to the staff having to attend to the washing, feeding, and excretory functions of so many patients strictly confined to bed. A totally new problem has now developed in handling the large percentage of ambulant patients. Most wards have no facilities for the patient who is not in bed. Suitably furnished day room, more toilet facilities, cafeteria systems, and dining room accommodation, with an increase in ward orderlies and access to physiotherapy and occupational therapy are now necessary.

The after-care of many patients can be managed by the family doctor. Stitches and small residual dressings could be done at home with less risk of cross-infection, if properly sterilized dressings were made available. At present the general practitioner has no sterile equipment, and a sterile dressing drum or disposable packet service for all practitioners would not be expensive. Much follow-up attendance at hospital out-patients is redundant, and has the subtle and adverse suggestion that the patient is not really cured.

The key to the management of the early ambulant patient lies in the closer contact of the general practitioner with the hospital service. If his patients are to be ambulant quickly the general practitioner should be present at more operations and visit his patients in the wards. He would then be in a better informed position to continue the process of rehabilitation at home.

The obstetric bed shortage could be solved by the early discharge of the puerperal woman on the fifth day, the remainder of the puerperium being conducted at home. The patient delivered at home can get up with the combined effort of doctor, nurse and home help on the first day, but one cannot help wondering to what extent doctors and midwives will be able to maintain proper interest if they are barred from attending confinements in hospital. The integration of general practitioner obstetricians into the obstetric team by the provision of more general practitioner obstetric beds and ready availability of the obstetric consultant is surely a corollary to the early ambulation and discharge of obstetric cases in hospital.

Last of all, the geriatric patient must not be allowed to stay in bed, if life of an agreeable nature is to continue. We all know how rapidly aged patients die if a fall produces a fracture that prohibits early ambulation. The pinning of fractured hips, and in suitable cases the introduction of a prosthesis such as a Moore's head, undoubtedly shortens the time spent in bed. Aged patients stand abdominal operations well if they are allowed up the day following operation. They recover even better if they are returned to their own homes as soon as possible, and here the general practitioner should be called into the picture early. Relatives of the aged are often unco-operative, and the doctor is the one person who can help press the issue. Once home, however, even with willing relatives, the patient must still be pressed into activity. It is so often at this stage that the patient is unwilling to continue the effort, and relatives do not appreciate that by allowing unnecessary bed rest the

whole of the effort to save the patient and bring back reasonable comfort is vitiated.

REFERENCES

ASHER, R. A. J. (1947) *Brit. med. J.*, ii, 967.
BRUMMER, P., LINKO, E., and KASANEN, A. (1956) *Amer. Heart J.*, **52**, 269.
JANUARY, L. E. (1956) *Iowa med. Soc.*, **46**, 337.
LEITHAUSER, D. J., and SARAF, L. (1953) *Surg. Clin. N. Amer.*, **33**, 1059.
PALUMBO, L. T., and PAUL, R. E. (1952) *Amer. Surg.*, **18**, 1128.

Mr. Bryan N. Brooke (Consultant, Birmingham):

The term early ambulation is a relative one: relative to the practices of the immediate past and to the operative injury sustained. Twenty years ago most surgeons felt ten to fourteen days' bed rest was necessary following partial gastrectomy. Now, ten to fourteen days represents the full hospital stay in most uncomplicated cases; the patient is usually up on the second or third day, even on the first post-operative day in some clinics. In the past, there was a correlation between the period of recumbency and the magnitude of the operation, based more on intuitive assessment than logical reasoning.

Early ambulation depends upon certain intrinsic factors, such as the initial disease, the severity of the operation, and the amount of pre- and post-operative medication and anæsthetic required. But the outcome of the equation is not mensurable in Cartesian terms. One element which we tend to forget is the degree of the patient's incapacity due to drugs, for although there is a strong tendency for the modern anæsthetist to bring the patient round on the operating table, anæsthetic drugs cause a "hang-over" for some time after consciousness is regained—a "hang-over" prolonged by post-operative medication in not a few who are sensitive to morphia.

To-day modern surgery is performed on those *in extremis* almost as an elective procedure, where hitherto it was only undertaken in emergency. It is important to recognize that the intrinsic factor of the disorder precludes ambulation until the phase of physiological recovery is reached. The post-operative patient without a serious pre-existing disorder passes through four phases of convalescence (Moore, 1958): (1) Injury, (2) the turning point, (3) restoration of strength (spontaneous normal anabolism), (4) fat gain phase due to redeposition. In phase 1 there is water and sodium retention due to the adrenal response to trauma (Moore and Ball, 1952); also nitrogen loss, depriving intrinsic stores and therefore inducing muscle wasting, which in turn is due in part to low intake and in part to an obscure effect, again probably hormonal, of trauma. These biochemical factors are perhaps indicative of the physiological background of a patient's disinclination to arise and walk and may be one reason why his wound has little tensile strength for the first two to three days. In cases with pre-existing malnutrition this phase is considerably prolonged. The clinical recognition of the onset of phase 2 is therefore important and the return to a more positive biochemical state is reflected in the patient's return of interest as shown by the application of lipstick by women and by the desire to shave by men.

The principle of early ambulation has now been accepted by most clinicians, as a result in part of the exigencies of rehabilitation in the last war and in part of the prolonged campaign over the last two decades to avoid femoral vein thrombosis and pulmonary embolism. The problem is now not whether ambulation should start at the first possible moment, but when that moment is reached in each case, and this depends upon the intrinsic factors described above.

Economically the efficiency of a hospital is related to the rapidity of the patient turnover. This is doubtless aided by early ambulation. Avery Jones (1959) showed that the increase in turnover in hospital beds has resulted in the equivalent of 140 new hospitals of 600 beds between 1949 and 1958. For example, in 1951 I had sixty hernia cases on my waiting list, with a waiting time just short of two years. By keeping one bed for hernia cases, operating on a hernia case twice a week and discharging to a convalescent hospital on the third or fourth day, it was possible to eliminate the waiting list in six months. Owing to the lack of convalescent hospitals (Ministry of Health, 1959) there is an opportunity for liaison with the general practitioner. After the St. Mark's operation for hæmorrhoids, healing takes three to four weeks at least and supervision for frequent dressings was required necessitating at least two weeks in hospital, if not more. I arranged for early return to home by informing the District Nurse of the area concerned, so that she could attend hospital to see the patient, learn what treatment was being given and continue it at home. The doctor was, of course, informed also. This has now become unnecessary because I sew up the wounds after hæmorrhoidectomy. However, this made me realize that in order to reap the benefit of early ambulation, namely early return home, all that was necessary was to ring up the doctor and explain. The doctor, too, can say whether the home circumstances are adequate, if this has not already been ascertained from the patient or his relations.

The advantages of early discharge from hospital, as the natural sequence of early ambulation, are more efficient use of hospitals, reduction of waiting lists, reduction of risk to the patient (e.g. infection), and psychological effects.

The difficulties of early discharge arise from the possibility of certain post-operative complications, difficult home circumstances and the difficulty of maintaining close contact with the general practitioner.

REFERENCES

JONES, F. A. (1959) *Lancet*, ii, 968.

Ministry of Health (1959) Convalescent Treatment. H.M.S.O., London.

MOORE, F. D. (1958) *Ann. N.Y. Acad. Sci.*, **73**, 387.

——, and BALL, M. R. (1952) Metabolic Response to Surgery. Springfield, Ill.

Miss Muriel Powell, S.R.N., S.C.N., D.N. (Matron, London), also contributed to the Discussion.

Meeting
February 17, 1960

DISCUSSION ON PROSTATECTOMY—EARLY OR LATE?

Dr. R. A. P. Paul (Hillingdon):

Apart from acute retention, few patients with prostatic obstruction are aware of any other symptoms. A retrospective enquiry showed that they had not appreciated a reduction in their urinary stream nor difficulty in starting the act. They may have noticed increased staining of their underpants but this was attributed to careless habits. Many men, for as long as they can remember, have got up at night but, apart from acute retention, nocturia three or more times each night is an indication for investigation and possible prostatectomy.

I would like to postpone prostatectomy in old men in the hope that surgery would be unnecessary. Many old men with cardiovascular and respiratory disease live for years with an enlarged prostate without acute retention, until a crisis is provoked and indeed produced either by anxiety or drugs. A respiratory case with moderate or fairly severe bronchospasm will remain well until the doctor goes on holiday and someone else comes to see him, then he loses confidence and has a spasm of the sphincter as well as the bronchioles. I have returned from holiday to find this on more than one occasion. Admission to hospital for other reasons than genito-urinary disease will often produce acute retention because of anxiety, and possibly the inability to pass urine when they want to do so. Old people are best left in their own homes in spite of all talk about geriatric clinics and eventide homes. Prostatectomy relieves symptoms but it does not prolong life a great deal if one has to contend with a hard winter and an influenza epidemic. Blood urea and the kidney condition at the time of operation are the real criteria and determine how long the patient will live. It is well to remember that in helping an old man with his bronchospasm, the too liberal prescription of ephedrine or belladonna precipitates acute retention.

Sometimes on referring patients to hospital, only comforting words are received in return, and little else is possible. There are times when I am forced by the patient to refer him to hospital even though the symptoms are minimal. In these circumstances I would prefer the consultant to send the patient back to me and not allow him to continue attending as an out-patient. A friend of mine attended a patient of 35 who had unbearable frequency and great difficulty in passing his urine. He was fully investigated and although everything appeared normal he demanded that "something would have to be done". My friend suddenly thought of chlorpromazine, which produced a cure after taking pills for one day.

A psychiatrist once told me that the two most pleasurable things in life were the acts of evacuation of the bowel and bladder. Certainly it must be pleasurable if you can manage it only after it had appeared impossible. However, whether it is pleasurable or not, we use the coldest room in the house for our pleasure. Thus an aged man, bronchitic and with congestive heart failure, goes to the coldest room in the house, to sit on the coldest seat to do the things which are most important to him.

The old man always prefers to sit down to micturate, because he is afraid that if he strains he will also open his bowels. He has to strain because he has lost the facility to relax, and this inability to relax is in my opinion a big factor in his respiratory condition. Sitting down is physically the wrong way to pass urine, as "the pipe line is above the tank". In addition tight clothes often restrict an already inadequate flow. The right and proper way to empty the bladder is on all fours, but for practical purposes standing up, leaning forward, is the next best alternative. I think that all men, and especially old men, should further empty the bladder standing up, even after sitting down to defæcate. This would prevent the residue being left in the bladder and the ensuing infection. I am extremely interested in this facility to relax. The asthmatic patient

relaxes and breathes easily, but if he is tense, his breathing becomes difficult. It is equally true to say that often the urinary stream is excellent, strong and full volume, and then as the patient becomes tense it is difficult and small. This relaxation is something that most people cannot think about, for if they think they become tense and the act becomes difficult. I am sure medicine must give more thought and consideration to teaching people to do the normal things in life relaxed, such as breathing, micturition and even walking.

The opportune time for prostatectomy must be early rather than late. It must be before the kidney efficiency has dropped too far, for it is my impression that this does not improve much afterwards. It is difficult to see these men early, as they are often not aware of the need of advice before they have retention. I think the general practitioner should be watchful of all his patients aged 50 and above, who have any tendency to bronchitis and cardiovascular disease. If these men have to get up three times or more at night, have difficulty in starting the stream and on *one* occasion after a long wait have had very great difficulty in starting the act, they should be investigated. If there is any loss of kidney efficiency they should have a prostatectomy. I have said that I try to avoid surgery in the more elderly aged 65 - 70 and upwards. I believe that many of these would do well with cystotomies but I would not care to have to look after them.

Finally, two doctor friends of mine have had their prostates removed at an early age, one before he was 50 and the other in the early 50's. One found that he was getting up so frequently at night that he had no rest and when investigation showed some loss of kidney function, he decided to have the operation. The other man could hardly sit through a match at Twickenham and although he did not have to get up at night, he had difficulty in starting micturition in the morning. Now he can see the entire Middlesex Seven-a-Sides without a shiver. What more could one ask for early prostatectomy?

Mr. Howard G. Hanley (London):

It is not the purpose of this paper to discuss the various types of operation or the long-term results following prostatectomy, but rather to decide when the operation should be performed. It is fair to state that most men if they live long enough, will require a prostatectomy, therefore this discussion is very relevant.

If there were definite signs and symptoms which would tell us that retention was eventually inevitable in our own particular case, we would, if sensible, opt for elective prostatectomy. It is important to define quite clearly the difference between a prophylactic and an elective operation. A prophylactic operation is performed to prevent the onset of some pathology which might never occur in any event, e.g. the routine removal of a normal appendix at the same time as, say, a hysterectomy. This is to ensure that the patient will never develop acute appendicitis. An elective operation is performed for established pathology, but it is performed at the optimum time under optimum conditions. There is no place for prophylactic prostatectomy because an adenoma cannot be enucleated before it has developed, but elective prostatectomy should be the operation of choice. Retention must be avoided at all costs. It is not the retention, with its temporary discomfort, which is so important, but the fact that retention only occurs after considerable damage has been done. It is the decompensation and ill-health leading up to retention which make it a point of no return. In a consecutive series of 214 prostatectomy operations in an acute general hospital, the operative mortality following retention of urine was 8% whereas in the absence of retention it was only 2·5%. This is a significant difference, and indicates the very poor general condition of the average patient with retention of urine.

To the urologist, it is the patient's general condition with regard to his cardiovascular, respiratory and central nervous systems which matters, rather than his renal function or his age in years. Only two of the 14 deaths in the series quoted were due to urinary complications. One was due to pyonephrosis and one to pyelonephritis, whilst the rest died from general medical causes, or from being "just too old". The two great hazards of prostatectomy have always been hæmorrhage and infection. So much so that in the past it has been necessary to weigh carefully the known risks of operative morbidity and mortality against the unpredictable risks of retention and renal failure. To-day the picture has changed considerably. The operative morbidity and mortality have been so greatly reduced that we should now be considering operation for convenience rather than for sheer necessity. To-day, using modern operative techniques and anæsthesia, blood loss has ceased to be a problem, and in a majority of cases is negligible, 3 to 6 oz or so measured by the most scientific means possible. Under such conditions, blood transfusion is a rarity, and because the improved hæmostasis makes completely closed drainage possible without the necessity of bladder washouts, infection can be adequately controlled. The point to be stressed here is that prostatectomy is not the terrible thing it was, and that there is

really no justification for postponing operation in the hope that it will not become an acute necessity.

Acute retention must be avoided at all costs. The reason for this, quite apart from the increased operative mortality, is as follows. As the prostate slowly enlarges, the bladder muscles hypertrophy, and for many years the emptying efficiency is maintained by this physiological balance. However, as soon as the bladder compensation fails, emptying is interfered with and a small quantity of residual urine is left after micturition. In itself this is of little consequence, but it is nevertheless a warning that the point of physiological compensation has been passed. Infection may now occur and the problems of ureteric reflux, renal back pressure and overflow incontinence follow in due course. It is most unlikely that acute retention due to prostatic obstruction will ever occur until the stage of decompensation has been reached. In other words truly acute retention is rare, as compared with acute following chronic retention, and it is almost invariably the final precipitating causes of the retention which are the danger, and not the stoppage *per se*. A classical and a contemporary cause of acute retention is alcohol, not a lot, but just enough! Pleasant analgesia, overfilling of a poorly compensated bladder and inaccessibility of the usual offices predispose to retention, but even here some measure of compensatory failure must be present to some extent before retention will occur.

The most dangerous form of retention from the urologist's point of view is that which occurs in a man who is already ill in bed with some medical complaint such as pneumonia, bronchitis, cardiac failure, &c., because once retention has occurred, prostatectomy is generally necessary eventually. This raises the question: prostatectomy, early or late? When should one decide that a man with moderate prostatic symptoms should have an operation? Ironically enough there is little doubt that the fitter a man is the longer he can afford to delay. It is the poor risk patient who should have an early operation before he becomes any worse. Unfortunately this is the type of patient who is deferred, just because he is unfit. Great age in itself is no bar to successful prostatectomy, and while urologists are always proud of their 90-year old patients, it is frequently forgotten that in order to live to 90 a man has to be tough, and many of these very old men stand operations very well indeed; infinitely better than a younger man who is medically unfit.

I am sure that most of us would agree that prostatectomy should be performed before retention occurs. Now this being so, why is it that of the 214 consecutive prostatectomies to which I have referred, over 70% were seen with acute retention? Even at St. Paul's Hospital where the beds available for emergency admissions are extremely limited, over 22% of the prostatic cases during the past year were admitted with retention, while 25 requests from the Emergency Bed Service to admit cases of acute retention were made during the month of January 1960—nearly one per day. In contrast to this, why is it so rare to see a private patient with acute retention? This cannot possibly be a question of economics, as prostatectomy costs the hospital patient nothing while for the private patient it is very expensive.

It is for the General Practitioners to record what happens to the patient between the onset of prostatic symptoms and the onset of retention. It has been said on numerous occasions that the patient is merely given a bottle of Mist. Pot. Cit. when he complains of nocturnal frequency, or other symptoms. I doubt whether this is true at all for I suspect that in the great majority of cases, the General Practitioner does not see these patients any earlier than the urologist does, and I think it is a matter of educating a rather misinformed public. Many men consider it normal to have difficulty, frequency, and dysuria as they get older. Moreover, not only are patients ignorant but they are also afraid of hearing the truth, namely that an operation will be necessary. We as a profession cannot escape from accepting the responsibility for an uninformed general public. We rise up in arms when the press or television tries to cast light upon various subjects, rightly perhaps, but I also think that we ourselves should be a little more open and forthcoming. The lead should come from us and not from the press. Such medical education of the public is a very difficult problem. Although we must discourage the 45- to 55-year-old man with mild chronic prostatitis from demanding "an operation" (which will not help him), we must nevertheless try to explain the dangers of chronic urinary obstruction, and in order to do this we must formulate our own views about the indications for prostatectomy.

The size of the adenoma is not necessarily related to the need for operation, but it is a sign which cannot possibly be ignored even if the patient has very few symptoms. 100 consecutive adenomata removed at St. Peter's and St. Paul's Hospitals have been analysed into groups according to age and weight. Now allowing for the fact that one 62-year-old man had a gland weighing 105 g, while one 89-year-old man's gland only weighed 35 g, there is no doubt whatever that, statistically, the longer we live the

larger the adenoma becomes. In fact it more than doubles in size between 65 and 75 years. The difficult decisions arise in a man with troublesome symptoms but a relatively small prostate on rectal examination. Diurnal frequency is not necessarily a symptom calling for operation. Nocturnal frequency, however, if it interferes with sleep will rapidly undermine health, while difficulty and dribbling are self-evident danger signals, and call for surgery. One attack of retention is sufficient for me to insist upon operation. Again I would repeat the question, what happens to the patient between the onset of his symptoms and his acute retention? If we can operate upon him early, there is no doubt whatever that the morbidity and mortality can be kept within reasonable bounds.

In conclusion I would like to pose certain questions to General Practitioners, which only they can answer:

(1) Apart from an attack of retention of urine, what do you consider to be the most important symptom calling for prostatectomy?

(2) Do you in your own practice urge a man to have his prostate removed (*a*) early *because* he has cardiovascular or respiratory disease, or (*b*) to postpone operation in the hope that he will never require surgery *because* he has cardiovascular or respiratory disease?

(3) What proportion of your frail old men have an illness which confines them to bed, *without* precipitating urinary troubles?

(4) We could halve our operative mortality by sending many of these men home with a permanent suprapubic cystotomy. What would the general practitioner feel about that? How many of you have patients with permanent cystotomies? Are tubes changed by (*a*) patient or relatives? (*b*) District Nurse? (*c*) General Practitioner? (*d*) Hospital?

(5) The "black month" for retention is February. This is also the worst month for respiratory disease. Urinary symptoms improve during the spring and summer months. Do you find that a man who has suffered from urinary troubles during one winter has similar trouble during the next winter, and if so should he be investigated during the summer months?

(6) When you send such a man to outpatients, whose symptoms are at the time minimal, do we send him back with "comforting words" only?

(7) Is a senile old man who has had his prostate removed years before, easier to manage than one who has not?

(8) Does removal of the prostate prevent any urinary complications in such frail old men?

Dr. Richard I. Bodman (London):

As an anæsthetist I am not in a position to decide when to operate—whether early or late; although I occasionally have to decide between very late and too late! My contribution to the discussion relates to the three most important factors which influence my assessment of the risks of this particular operation, hoping that this may help general practitioners to decide when or whether their patient should have a prostatectomy. These factors are old age and its two concomitant complications, cardiovascular disease and respiratory disease.

What do we mean by old?—Fig. 1 shows the ages of those patients who attended Hillingdon

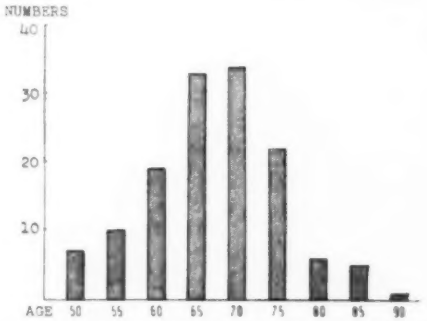


FIG. 1.—Age distribution of 137 patients requiring treatment for urinary obstruction. Average age is 69 years.

Hospital last year for treatment of urinary obstruction and demonstrates why prostatectomy is an operation of old age. They extend from 50 to 90, the mean being 69. This being so one must not only assess the patient's likelihood of surviving the operation, but also decide whether his expectation of life is sufficient to justify the physical and mental trauma involved and whether he will live long enough to derive some benefit from the operation. With regard to the natural expectation of life I have in the past subconsciously adopted the Psalmist's "three score years and ten" and tended to think that anyone over 70 is lucky to be alive anyway. The Registrar-General's reports, however, show a more optimistic state of affairs, for although at the age of 25 the expectation of life is in fact 45 years (to 70), paradoxically a man reaching the age of 70 can expect to live another 9 years and at 75 can expect to live to 82. I wonder if surgeons when they decline to operate have these figures in mind. Is there then any age which contraindicates surgery? I suppose at the age of 100 when the expectation of life is a matter of months, prostatectomy would hardly be justified; but we have removed the prostate from a man

of 90 and when last heard of he was fishing in Scotland. In general, though, I believe that in those series of prostatectomies which have been published, the patients who have not survived the operation tended to be the older ones. The reason for this is to be found in Table I, which

TABLE I.—CAUSES OF DEATH (ALL MALES)
(during five years—1949–53)
Registrar-General's Decennial Supplement 1951, Occupational Mortality, Part II, Vol. 2, p. 21)

Age—	65–69	70–74	75 +
Malignant neoplasms (all)	36,000	36,000	49,000
Vascular lesions of C.N.S.	20,000	28,000	61,000
Coronary disease	32,000	33,000	46,000
Hypertension	7,000	9,000	17,000
Other myocardial degen.	15,000	27,000	103,000
Gen. arteriosclerosis	3,000	5,000	18,000
Pneumonia	6,000	7,000	17,000
Bronchitis	16,000	17,000	31,000
Hyperplasia of prostate	3,000	5,000	14,000
All other causes	35,000	34,000	72,000

Numbers to nearest 1,000.

shows the progressive increase in cardiovascular disease and respiratory disease with age, and is confirmed by the observation that death following prostatectomy is more often than not due to cardiovascular or respiratory complications, rather than to the hazards of the condition itself. So although we all know of patients who are hale and hearty at 80, these are exceptions to the rule that the older you get the more likely are you to suffer from the complications of old age. My conclusions about age are obvious enough, it is better to operate at 65 than at 75; but at 75 it is still worth operating, for your patient may have another seven years to live!

Cardiovascular disease.—At least a fifth of all patients coming to prostatectomy at Hillingdon had a history of hemiplegia or coronary thrombosis, or were found to be suffering from angina pectoris or severe hypertension, and auricular fibrillation was a common finding. At one time we had ECGs done on all patients and I used to make a point of not looking at them until the operation was safely concluded. As a result of experience I now regard them with greater equanimity. The following is a fair sample of the cardiologist's expertise: "ECG shows a fairly extensive atrio-septal infarct and the marked deviation of ST in lead V_4 suggests that he may have a localized aneurysmal dilatation of the ventricular wall." In fact this man, aged 73, had had a coronary thrombosis six months before and he was short of breath on exertion and had a mild chronic bronchitis. He had an uneventful operation and recovered very well. Unfortunately, the ECG cannot detect when a patient is *going to have* a coronary thrombosis and we have had patients die of a coronary thrombosis the day before operation and one on the day before he was due for discharge, after an uneventful prostatectomy. The former is unfortunate but the latter puts up the mortality figure for prostatectomy. These are hazards which must be faced when operating in this age group.

Is an ECG a waste of time? This is not so, as to be forewarned is to be forearmed. But it should take its place after a clinical assessment. In my experience the most important guide to a patient's fitness is his exercise tolerance, based on his walking habits at home or in hospital. This can be assessed by how far he can walk without getting out of breath, his ability to walk upstairs, and whether he can walk and talk at the same time. Provided the man can get about and there is a reasonable expectation of his condition being improved by prostatectomy, then we regard him as fit. What about heart failure? This depends on his response to treatment. If he improves then we can operate. In fact our experience leads me to the conclusion, confirmed by our cardiologist at Hillingdon, that cardiovascular disease, including coronary disease, is not a contra-indication to prostatectomy, provided of course that anoxia is not allowed to occur and that blood loss is measured and replaced. You may ask why we feel confident about this. The answer is that during an operation with a properly conducted anæsthetic, the patient lies supine, his muscles relaxed, and he may not even have to breathe for himself: in fact his basal metabolism is lower than at any other time: the heart consequently has less work to do and, provided it receives adequate oxygen, is under less stress than usual. A defective myocardium which can barely cope with the restricted activity of a "cardiac" life is better off under anæsthesia than during consciousness.

Respiratory disease.—Having noticed how many of our old men seem to have a chronic cough, I recently looked for some figures that might show a correlation between chronic bronchitis and enlargement of the prostate. Turning up the tables of deaths by social classes in the Registrar-General's reports and using

TABLE II.—CAUSES OF DEATH BY SOCIAL CLASSES AT AGE 65 AND OVER
(Proportionate Mortality Ratio)

Social Classes—	I Profes-sional	II Inter-mediate	III skilled	IV Partly skilled	V Unskilled	All
Coronary disease	144	115	101	87	84	100
Bronchitis	51	73	103	106	130	100
Hyperplasia of prostate	127	123	99	94	76	100

Registrar-General's Decennial Supplement 1951, Occupational Mortality, Part II, Vol. 2, pp. 21–27.

coronary thrombosis as a guide, for we all know this is more common among the professional classes, I extracted the foregoing table (Table II). Status-seekers who are having trouble with their water will be gratified to see that hyperplasia of the prostate has a distribution similar to coronary thrombosis. Bronchitis on the other hand has not. One interesting observation to be drawn from this "negative correlation" between chronic bronchitis and hyperplasia of the prostate, is that if you draw your patients from social classes IV and V, the number with chronic bronchitis is likely to be higher than in the general population.

Disease of the respiratory system is of particular interest to the anæsthetist for two reasons. First, if the lung function is severely restricted, as in severe emphysema or acute asthma, the patient may come to depend on his accessory muscles of respiration to stay alive. If such a patient is rendered unconscious his voluntary efforts will cease and the automatic movements of his diaphragm may be insufficient to maintain his exchange of oxygen and carbon dioxide. If we now paralyse this patient with the object of artificially ventilating him, we may find that we can inflate his chest, but that he fails to expire owing to loss of elasticity of the lungs in emphysema, or to spasm of the air passages in asthma. An attempt to apply a negative pressure with a respiratory pump can result in collapse of the air passages and trapping of the air in the alveoli. Secondly, most old people with poor lung function have a complicating chronic infection. This acts as a reservoir from which an acute and possibly fatal infection can easily arise after operation.

Two measurements can be of great help in diagnosing and treating such complications. The first is simply to measure how much air the lungs will hold, namely the vital capacity. The second is to measure the rate of flow of air from the lungs, and this will reflect the patency of the air passages, for the rate of flow of air, like that of water, is proportional to the diameter of the tube through which it flows. The more constricted the air passages the slower the expiration. The vital capacity is easily measured with a spirometer or more portably with a gas meter such as the Draeger. It is more useful if the actual measurement can be related to the expected figure for a given age, height and weight. I have constructed a table which, with the aid of the body surface area nomogram, gives such a figure. Workers in this field accept a wide individual variation so that a range of $\pm 20\%$ may still be within normal limits. It is of interest to note that the expected vital capacity diminishes by 50% at 80 years of age. The second measurement, the rate of flow of air, can be measured by using the spirometer together with a revolving drum. The subject makes a forced expulsion of air into the spirometer and this is recorded. The measurement can be expressed in ml per sec and is then called the Forced Expiratory Volume (F.E.V.). Such an apparatus is bulky, not very portable and a little capricious and for clinical use the Wright peak flow meter has much to recommend it, as it is convenient and portable and seems to give very consistent results. An even simpler test is the candle test. The subject is asked to blow out the candle and if he is unable to do this at 12 in. from the mouth he should be investigated further. Unfortunately, this test depends to some extent on how wide the mouth is opened, so I have modified it slightly to regulate the size of the orifice through which the subject blows and by arranging the candle on a slide, I have made it rather crudely quantitative (Fig. 2).

FIG. 2.—A simple quantitative candle test.

By using these last three tests before and after inhaling a bronchodilator drug further information can be obtained. An improved performance after the bronchodilator drug is prima facie evidence of bronchospasm, whereas no change in a poor performer indicates an emphysematous condition.

Bronchospasm is amenable to treatment with bronchodilator drugs such as Choledyl 200 mg 1-2 tabs. four times a day by mouth, or adrenaline and atropine spray, B.P.C., three times a day by inhalation. Chronic infection is treated with postural drainage with percussion twice daily for at least a week. The sputum is cultured and the appropriate antibiotic prescribed. Fortunately a pure emphysematous condition is rarely found on its own, for it does not respond to treatment. What influence will respiratory disease have on

your decision whether or not to operate on your patient with an enlarged prostate? The answer is the same as for heart failure: provided he makes a good response to treatment, operation may be undertaken at once. If it is decided to postpone operation it must be borne in mind that the chest condition will probably progress each year, with the possibility of acute exacerbations each winter.

For the sake of clarity we have discussed old age, cardiovascular disease and respiratory disease separately, but very often an old man presents in the medical wards with a combination of bronchitis and heart failure. He is put to bed and promptly gets acute retention. This syndrome may be thought of as a vicious circle, with chronic bronchitis and chronic retention as underlying contributory factors. Various things can initiate the syndrome such as an attack of *acute* bronchitis: undue exertion in the elderly may be too much for the heart. Putting the patient to bed for any other reason, or unwise treatment of bronchospasm with ephedrine may cause an acute retention, and the vicious circle is started. Fortunately the conditions are amenable to treatment: a catheter for the acute retention, antibiotics for the pneumonia and digitalis for the heart. If the patient responds to treatment, operation will eliminate one factor in the vicious circle, when he suffers another "attack" next winter.

Summary.—All the conditions discussed progress with age. The cardiovascular system becomes more atherosclerotic, the vital capacity and forced expiratory volume diminish, chronic bronchitis supervenes and presents a greater hazard each winter. But still at the age of 70 a man may have nine years to live and at 75 he can expect seven years more, so why not remove his prostate and relieve him of one burden before he ends his days?

Meeting
March 16, 1960

A DISCUSSION on **What is a Family Doctor?** was held.

The opening speakers were Dr. WILLIAM W. FULTON, who spoke on **A General Practitioner's View**; Dr. HARVEY FLACK, on **The Point of View of the Public**; and Sir FRANK NEWSAM, who spoke **From the Patient's View-point.**

Meeting
April 20, 1960

TRANSATLANTIC DISCUSSION ON CASES OF PAIN OR FEVER

THIS meeting took the form of a Transatlantic Clinical-Pathological Conference between the Section of General Practice of the Royal Society of Medicine and the Delaware State Medical Society, Wilmington. The British team consisted of **Dr. Ian Watson** (General Practitioner), **Dr. John Richardson** (Physician), **Mr. Gordon Gill** (Surgeon), with **Dr. G. O. Barber** (General Practitioner) in the Chair.

The American team consisted of **Dr. Lemuel McGee** (Medical Director), **Dr. Leonard Lang** (Physician), **Dr. Dewey Nelson** (Neurologist), **Dr. John Howard** (Pathologist), with **Dr. G. Barrett Heckler** (Director of Medical Education) in the Chair.

The case presented by the British team was that of a 32-year-old man complaining of pain in the right loin, vomiting, frequency, nocturia and hæmaturia. Chest X-ray revealed a miliary type of lesion and he subsequently developed signs of central nervous involvement, although the cerebrospinal fluid remained normal. He eventually died in coma.

The members of the American panel considered the alternative diagnoses of either a granulomatous lesion, or a pulmonary or renal tumour with metastases to the meninges. The post-mortem findings showed a tuberculous abscess in the right kidney with spread to the meninges.

The American case was that of a 57-year-old man complaining of episodes of hæmoptysis and gastro-intestinal bleeding. Subsequently lymphadenopathy developed and the blood picture showed a marked leucocytosis. He was eventually treated with ACTH, but rapidly deteriorated and died. The British team discussed the varying aspects of the case and came to the conclusion that chronic leukæmia was the most likely diagnosis. Post-mortem examination showed miliary tuberculous lesions throughout the body, a finding quite unsuspected in life.

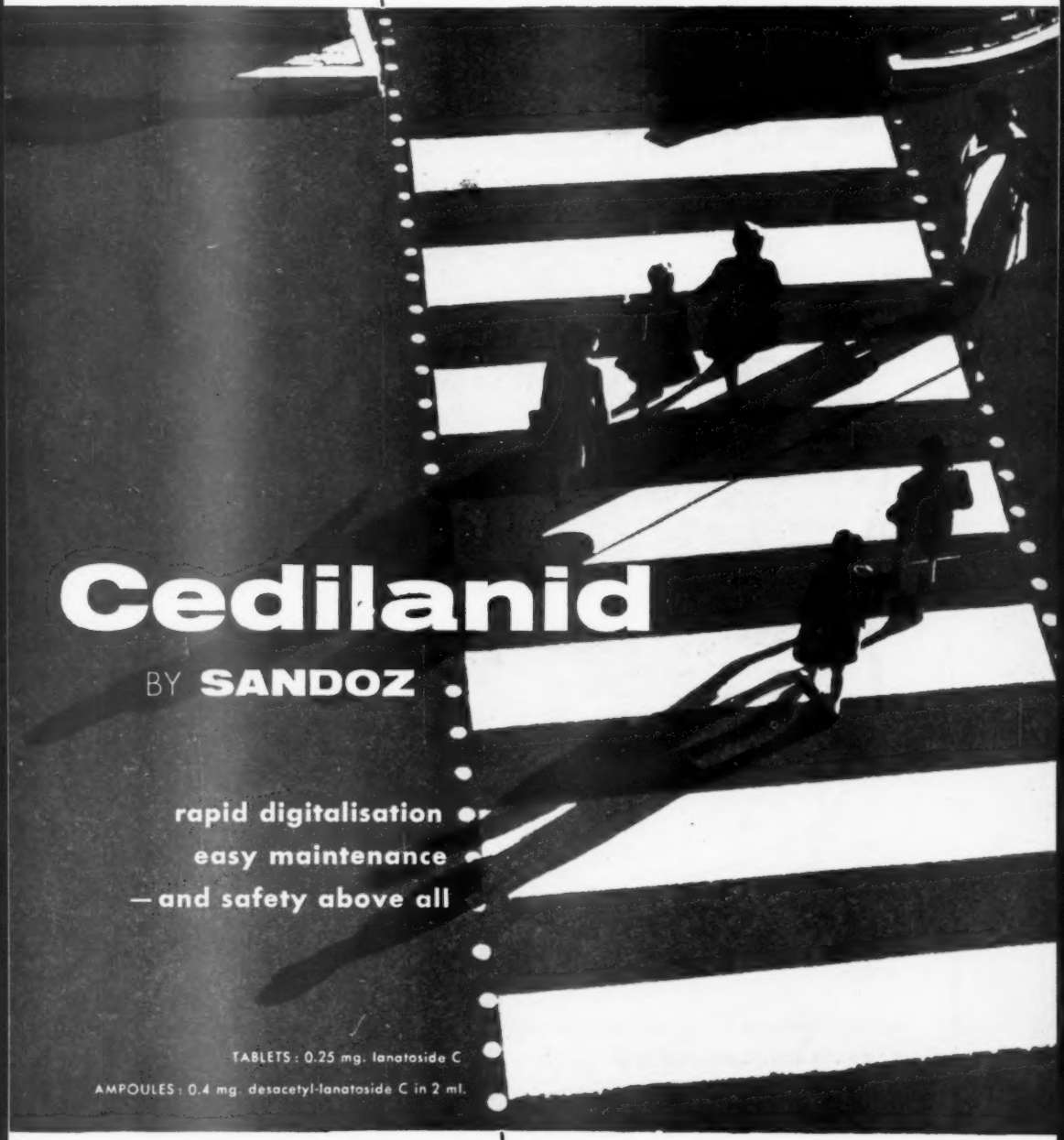
Dr. G. O. Barber, in summing up, remarked that thirty years ago tuberculosis had the name of "the captain of the men of death" and that it was a very salutary reminder that this disease had not lost its power by any means.

Meeting
May 18, 1960

THE RIGHT REVEREND THE LORD BISHOP OF DURHAM delivered an address on **The Relation between Parish Priest and Family Doctor.**

(*See The Practitioner*, 1960, **185**, 99.)

In the treatment of cardiac failure ...



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— British Encyclopaedia of Medical Practice, **6,** 407

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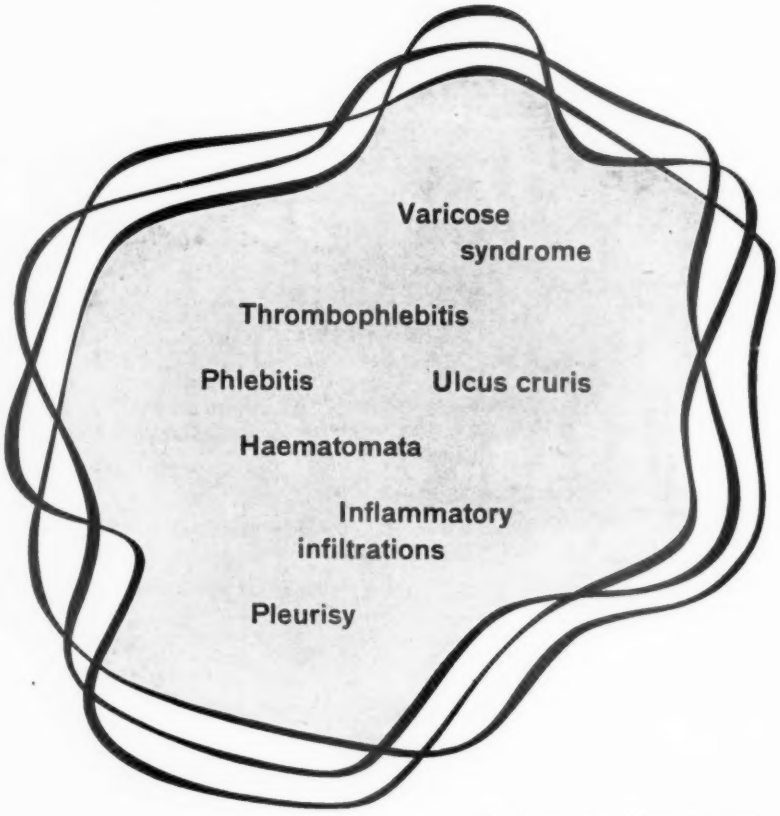

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Meeting
January 22, 1960

MEETING HELD AT THE ROYAL FREE HOSPITAL, GRAY'S INN ROAD, LONDON

Intra-oral Excision of the Submandibular Gland

By D. DOWNTON, F.D.S., and G. QVIST, F.R.C.S.

London

THE submandibular gland can be easily exposed through the mouth by incision of the mylohyoid muscle. One of the authors (D. D.) has frequently noted this during the operation of resection of the mylohyoid ridge as a surgical aid to the prosthetic problem of the atrophied lower alveolar ridge (Downton, 1954). This operation has been extended to the deliberate excision of the chronically inflamed salivary gland as an alternative to the standard cervical approach. The advantages of this technique are the avoidance of an external scar and of injury to the mandibular branch of the facial nerve.

The anæsthetic is administered by intranasal intubation and the throat packed as for any other intra-oral operation. In the edentulous patient, a curved incision is made through the muco-periosteum along the alveolus from the retro-molar pad to the canine region (Fig. 1). Where

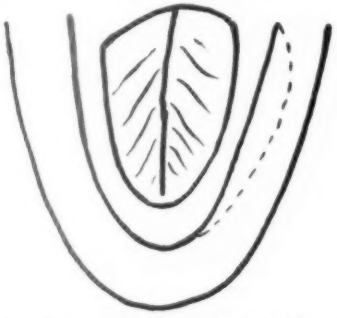

FIG. 1.—Incision shown by dotted line.

molar teeth are present, the incision is carried round the lingual side of the necks of the teeth. The mucoperiosteum is reflected medially (Fig. 2). If the mylohyoid ridge is pronounced, it is removed with a chisel; otherwise the muscle is separated from its attachment to the mandible.

On retraction of the separated mylohyoid muscle, the submandibular gland is seen and the anterior portion exposed by blunt dissection. The gland is rendered more prominent by digital pressure applied beneath the lower border of the mandible by an assistant (Fig. 3). Delivery of the gland into the wound is usually easy, but occasionally inflammatory adhesions necessitate a more prolonged dissection.

When the body of the gland is seen, it is gripped with tissue forceps and pulled up through the incision. The loop of the facial artery is demonstrated by blunt dissection and can frequently be freed completely from the gland. Occasionally, however, it has been necessary to divide it between ligatures. The lingual nerve can be seen through the distal

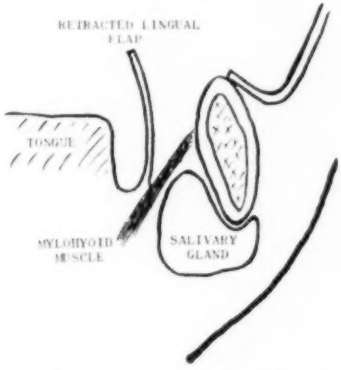

FIG. 2.—Mucoperiosteal flap reflected.

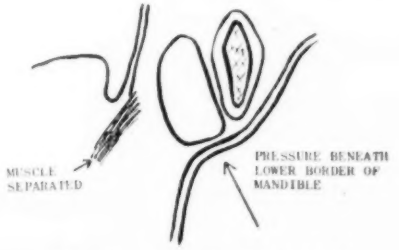

FIG. 3.—Mylohyoid muscle divided.

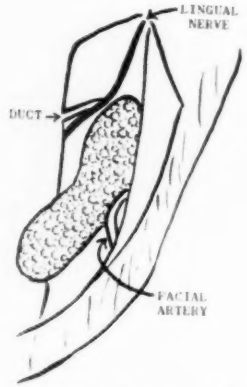

FIG. 4.—Intra-oral delivery of gland.

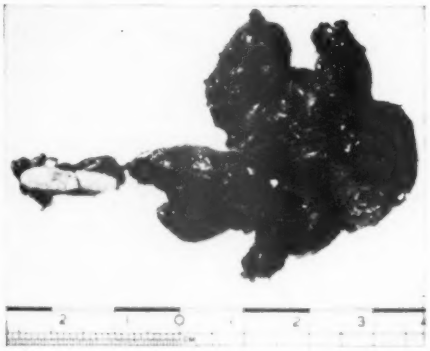

FIG. 5.—Showing calculus in duct; complete excision of gland.

part of the incision passing forwards and medially across the submandibular duct (Fig. 4). It is possible to follow the duct forward to its termination and remove it completely if necessary (Fig. 5).

When the molar teeth are present, the operation is a little more difficult and it is sometimes necessary to make a small cervical incision (2 cm) so that a finger can be inserted to give a greater upward pressure directly on the gland.

After the gland has been removed, the mucoperiosteal flap is sutured back loosely into place on to the mucoperiosteum of the alveolus with interrupted silk sutures. In the first 2 patients a drain was inserted, but in the remaining eight no drainage was instituted and post-operative infection occurred in 2 and had to be drained.

Post-operatively there has always been a hæmatoma in the submandibular space which has resolved within three or four days and one patient had paræsthesia lasting for three or four days along the side of the tongue due, probably, to contusion of the lingual nerve by retraction. These operations have been carried out under penicillin cover—1 mega unit of penicillin twice daily for five days.

All patients recovered quickly and were discharged from hospital within eight days and there was no damage to the mandibular branch of the facial nerve or to the hypoglossal nerve.

REFERENCE

DOWNTON, D. (1954) *Dent. Rec.*, **74**, 212.

The following papers were also read:

Recurrent and "Inoperable" Cancers.—Mr. H. DAINTREE JOHNSON.

Melanoma in Relation to Pregnancy.—Miss P. A. GEORGE.

Plasma Glucuronidase Levels in Breast Cancer.—Mr. B. L. WHITAKER.

Observations on Renal Homotransplantation.—Mr. R. Y. CALNE.

Anatomy of the Finger Joints and the Position of Function.—Mr. R. L. G. DAWSON.

Surgical Treatment of Acquired Heart Disease Utilizing the Pump Oxygenator.—Dr. C. W. LILLEHEI.

Clinical Cases and Specimens were demonstrated by the Surgical Staff of the Hospital.

The following demonstrations were given:

A New Method of Stereotaxis.—Mr. A. M. H. BENNETT.

Pituitary Ablation.—Mr. E. J. RADLEY SMITH and Mr. A. M. H. BENNETT.

Renal Response in Urinary Diversion.—Mr. JOHN HOPEWELL.

Electromyography in Nerve Injury.—Department of Physical Medicine.

Relations of the Recurrent Laryngeal Nerve.—Department of Anatomy.

Survey of Atheroma in the St. Pancras Area.—Department of Pathology.

Exfoliative Cytology in Gastric Carcinoma.—Department of Pathology.

Portal Hypertension.—The Medical Professorial Unit.

Magnesium Deficiency in Gastro-intestinal Surgery.—Department of Chemical Pathology.

Meeting
February 3, 1960

The Surgical Aspects of Non-malignant Strictures of the Bile Ducts, with Special Reference to Post-operative Strictures [*Abridged*]

PRESIDENT'S ADDRESS

By RODNEY MAINGOT, F.R.C.S.
London

Introduction

THE non-malignant strictures of the bile ducts, which are sometimes termed benign or simple strictures, are comparatively rare. Fully 90% of them are due to operative trauma of the bile ducts during cholecystectomy for gall-stones, exploration of the biliary passages in cases of choledocholithiasis, partial gastrectomy by the Billroth II method for penetrating duodenal ulcer, or excision of a diverticulum of the second portion of the duodenum. The remaining 10% of benign ductal strictures are caused by fibrosis of the sphincter of Oddi, primary sclerosing cholangitis, choledochoduodenal fistula due to stone or duodenal ulcer, or by congenital lesions such as atresia of the bile ducts or choledochus cyst.

The benign or simple strictures of the bile ducts may be classified as follows:

A. *Congenital:* (1) Atresia. (2) Choledochus cyst.

B. *Trauma:* (1) Penetrating. (2) Non-penetrating. (3) Operative—after (*a*) cholecystectomy, (*b*) bile-duct operations, (*c*) gastrectomy, (*d*) duodenal diverticulectomy.

C. *Primary sclerosing cholangitis.*

D. *Fibrosis of the sphincter of Oddi.*

E. *Fistula*—choledochoduodenal due to stone or duodenal ulcer.

F. *Extrinsic pressure*, e.g. chronic pancreatitis.

This address deals with three of these subjects: (1) Congenital atresia of the bile ducts. (2) Choledochus cyst. (3) Post-operative stricture of the bile ducts.

CONGENITAL ATRESIA OF THE BILE DUCTS

Not more than 20% are amenable to surgical treatment. One or more parts of the external biliary tract are either absent or exist as fibrous cords. The extent of such obliteration determines the operability of the case.

The clinical picture is similar in most cases. The outstanding symptom is *jaundice* which is present at birth or appears shortly afterwards. This is at first mild, the skin being merely tinted pale yellow, but it gradually increases until at the end of a month or so it is very intense and gives place to a greenish-yellow hue. The cirrhotic liver at the same time slowly enlarges and feels unduly hard on palpation, its edge being rounded and firm. The spleen is usually palpable. The stools are white, putty-like and acholic, while the urine is bile-laden and dark brown. It should be noted that the stools are always white from birth even though jaundice may not be noticed until the second or third week of life. The icteric index varies in different patients and from day to day in the same patient, ranging mostly between 50 and 200; the blood picture shows a secondary anæmia; the red cells are not unduly fragile, there is no microspherocytosis; the clotting time is seldom increased; the prothrombin values may be somewhat lowered; and the liver function tests all support a diagnosis of *obstructive jaundice.*

The condition may be confused with icterus neonatorum, erythroblastosis fœtalis, jaundice of hæmolytic sepsis, obstruction of the bile ducts by biliary mud or sand, congenital syphilis or familial hæmolytic anæmia.

Every attempt should be made to reach a diagnosis within the first four weeks of life and not to delay operation beyond the second month, as the majority of patients will die within six months if the obstruction is not relieved. A few patients, however, with complete congenital obstruction of the bile ducts have lived to be 9 to 24 months old.

The diagnosis can be arrived at with a fair degree of certainty by the end of the first month

of life by a process of elimination, and sometimes much earlier than this. In other words, the diagnosis is arrived at with considerable certainty by excluding other causes of jaundice and by proving that the patient under investigation is undoubtedly suffering from obstructive jaundice.

The mortality of the patients with complete obliteration of the bile ducts is obviously 100%. Gross (1953) recorded 146 cases; in 119, nothing could be done on surgical exploration; in 27, the gall-bladder, hepatic duct or common duct was available for anastomosis to the duodenum or stomach, and of these 12 were cured.

I can find records of only 3 cases of congenital atresia of the bile ducts successfully treated by surgery in this country. These were those of Beavan and Duncan (1946), Durell and Halliwell (1952) and a personal case (Maingot, 1955). To date only about 40 patients have been cured by some type of biliary intestinal anastomosis. In those instances the operation has consisted of anastomosing the bile duct (or gall-bladder) to the first portion of the duodenum, to the stomach, or to a loop of proximal jejunum.

Choledochus Cyst, or Congenital Cystic Dilatation of the Common Bile Duct

The condition is a congenital one and probably depends upon inequalities in the rate of epithelial proliferation during the stage of occlusion of the primitive choledochus. The epithelium is generally absent in the lining of the cyst wall, which is composed of dense fibrous inflammatory tissue. 96 cases were reported by Alonso-Lej *et al.* (1959). Up to date over 400 authentic cases have been recorded and a further 20 doubtful ones.

Although the distal portion of the common duct is generally narrowed or stenosed, a great diversity of findings in this region has been reported: valve folds, abnormal course of the duct through the duodenum or one or more kinks in its course. In a number of instances the calibre of the terminal end of the bile duct has been adequate.

The disease is congenital in origin, the Japanese race and the female sex being particularly affected. 82% are under 30 at the time of operation. Pain, jaundice and epigastric mass constitute the classical diagnostic triad. As a rule, the signs and symptoms of biliary obstruction, pressure effects on adjacent viscera and biliary cirrhosis are intermittent, but progressive in their severity. A painless ovoid or rounded mass can often be felt in the right upper quadrant of the abdomen. Excretion pyelography, intravenous cholangiography and barium examination of the stomach and duodenum are necessary as the disease mimics mucocele of the gall-bladder, cyst of the head of the pancreas, right hydronephrosis or hydatid disease of the liver.

Operative Treatment

Removal of the cyst (and gall-bladder) with anastomosis of the stump of the hepatic duct to the duodenum or jejunum is the treatment of choice. Choledochocystojejunostomy (combined with entero-anastomosis) has a low mortality and morbidity and is considered by most authorities to be an adequate procedure, although subsequent contraction of the stoma and biliary cirrhosis are not uncommon.

Before the advent of antibiotics, the operative mortality of cysto-enteric shunts was high—in the region of 30%. In recent years this has been reduced to about 10%, but 30% have recurrence of symptoms following operation and the majority of these succumb to biliary cirrhosis and portal hypertension within a period of three years.

The death-rate following excision of the cyst combined with hepaticojejunostomy (and jejunojejunostomy) is approximately 15%, but the late results are superior and more permanent than those which follow Roux-Y choledochocystojejunostomy.

Post-operative Strictures of the Bile Ducts

Post-operative stricture of the bile duct is one of the most tragic complications seen to-day in the practice of abdominal surgery.

The occurrence of a bile-duct stricture is a catastrophe not only to the patient but to the surgeon who performs the operation. The extent of the tragedy can be gauged by remembering that 70% of the patients are women under the age of 50, and that only about 60% are permanently cured by a reconstructive procedure.

It is estimated that some 30% of such patients will eventually die from the attempts made to repair the stricture or from the effects of intermittent or complete biliary obstruction. Many have had several unsuccessful operations for relief of the obstruction before being referred to a specialist in this field. Patients have been sent to me, deeply jaundiced and cirrhotic, who had had as many as six or seven previous operations for the correction of strictured ducts.

It is impossible to estimate the incidence of post-operative stricture of the bile passages, but

there is no doubt that injuries of the common duct related to cholecystectomy have increased, and it cannot be questioned that the number of common-duct injuries is much too great. Cattell and Braasch (1959) have recorded a series of over 1,000, and at the Mayo Clinic the yearly average number of such reconstructive operations is about 80.

This lecture is based on the experience gained in performing 98 operations upon 67 patients for bile-duct strictures during the last twenty-five years.

About 80% of all benign or simple strictures of the bile ducts are the result of surgery and this unfavourable aspect of surgery of the gall-bladder is sometimes used by physicians to justify conservative measures for the patient suffering from gall-stones with minimal or no symptoms. Statistics show that cholecystectomy for calculous cholecystitis, with or without exploration of the bile ducts, yields excellent results in about 85%, and that the operative mortality is low, rarely exceeding 1% in uncomplicated cases.

The operative death-rate in surgery of the biliary tract is related to the *delayed* treatment of gall-stones and to the incidence of jaundice and/or choledocholithiasis. As more and more patients are subjected to cholecystectomy, an increasing number of common-duct strictures are observed, not only in this country but also abroad, notably in America. Almost invariably they are avoidable.

The grave consequences of stricture of the bile duct do not rest entirely on the extreme and protracted morbidity but also on the frequent necessity for one or more repair operations with their attendant economic loss and distress and on the immediate and delayed post-operative mortality.

It is more important to continue teaching the method of *prevention* of these strictures than it is to detail technical methods of reconstructing the bile duct. The seriousness of these surgical mishaps is so great that minute attention to the details of operative procedures on the biliary tract should be constantly stressed.

Causes

For the sake of convenience, the causes of post-operative stricture of the bile ducts are best discussed under the following headings:

(1) *Hæmorrhage from the cystic artery, from an accessory cystic artery or from the right hepatic artery during excision of the gall-bladder.*—Bleeding from the cystic artery or from an accessory cystic artery can be controlled by Pringle's method, which consists in inserting the index finger of the left hand into the foramen of Winslow and then compressing the structure in the free border of the gastrohepatic omentum, when the bleeding point can be visualized, picked up and ligated with relative speed and security.

It is possible to divide the *right hepatic artery* inadvertently when it runs parallel with and close to the neck of the gall-bladder before giving off its stumpy branch—the cystic artery; or, again, in retrograde cholecystectomy, the curving right hepatic artery may be rendered taut or acutely angulated, and if a hæmostat is applied to the cystic duct in such cases, the lower end of the right hepatic artery will be tied to the cystic duct, while the top end will retract into the hidden recess behind the common hepatic duct and into the depths of the portal fissure. In this latter situation, the hæmorrhage is most difficult to control by any method, and the identification and secure ligation of the retracted upper end of the artery requires great skill.

As I have frequently stated, brisk bleeding from one of these arteries, a pool of blood, and a blind plunge with a hæmostat for the spurting point, will frequently lead to a number of tragic events.

(2) *The easy cholecystectomy.*—The easy cholecystectomy, during which too much traction on the gall-bladder and cystic duct has led to tenting of the common ducts and to ligation and excision of a segment of these ducts. The easy case in a visceroptotic patient with a loosely attached gall-bladder, the hurried operation, and the over-confident surgeon lacking in technical skill, all constitute a poor combination.

(3) *The difficult cholecystectomy.*—Cholecystectomy is indeed a most difficult undertaking in cases where the gall-bladder is small, shrunken, fibrotic and partly calcified, and lies high up close to the hilus of the liver. It often abuts against the common hepatic duct or the right hepatic duct, the planes of cleavage are difficult to identify, the arteries are distorted and are encased in a sheaf of dense fibrous tissue, and in some instances there may even be a fistula between the gall-bladder itself and the duct.

In such difficult cases it is advisable to open the common bile duct below the cystic duct, where it is readily accessible, and to insert a Liston sound into the right hepatic duct, this sound serving as a useful guide to the surgeon during his dissection.

Again, in some cases of acute cholecystitis the ducts may be unapproachable owing to the density of the adhesions and complete obscuration of the ducts and vessels by œdematous tissue. In such instances the wise surgeon will play for safety and perform cholecystostomy rather than blindly excise the inflamed organ or carry out a partial cholecystectomy.

The surgeon has to be on his guard also, where the cystic duct opens into the right hepatic duct; where it is unusually long, emptying its contents into the retroduodenal portion of the choledochus; and where no cystic duct is present, i.e. where the neck of the gall-bladder opens directly into the main ducts.

(4) *Suturing the cut edges of the right margin of the gastrohepatic omentum too tightly over the bile duct after cholecystectomy or choledochostomy.*—It is inadvisable to suture this omentum over the small area occupied by the stump of the cystic duct and the cystic artery as, should there be any post-operative bleeding or discharge of bile, these fluids will accumulate in the retroperitoneal tissues occupied by the bile duct. Should infection supervene in this space, the subsequent fibrosis may lead to stricture formation.

(5) *Slipping of the ligature which has been applied to the cystic duct and/or the inadvertent division of an accessory hepatic duct.*—In such instances a localized collection of blood and infected bile may pool and surround the ducts and in time cause a dense fibrous contraction of these passages. Bile is not only a cytolytic agent, but also a well-known sclerosant.

It seems probable to me that some of these cases of post-operative stricture of the bile passages are due to destruction of the bile ducts by the necrotizing effect of bile that has collected in the peritoneal cavity and pooled in the region of the ducts. The necrotizing and cytolytic effects of bile salts were demonstrated by Flexner and others many years ago, and have been amply confirmed. Dragstedt and Woodward (1952) believe that damage to the ducts is often due to some agent, such as bile, acting from without, rather than to some process acting from within, or to impairment of the blood supply.

(6) *Mutilation or perforation of the common duct during the process of exploring it for stone or for fibrosis of the sphincter of Oddi.*

(7) *During partial gastrectomy for a penetrating duodenal ulcer the lower end of the common bile duct is in danger of being damaged by knife, clamp or suture.*—About 3% of all bile duct strictures are observed after partial gastrectomy for the "difficult" duodenal ulcer.

(8) *A lack of anatomical knowledge and of the appreciation of the anomalies of the bile ducts and cystic artery.*

The Consequences of Bile-duct Injuries

About 15% of injuries to the bile ducts are recognized during the conduct of operation. The correct treatment here is immediate reconstruction, preferably by an axial union between the ends of the duct, and T-tube splintage of the anastomosis—choledochostomy. The remaining 85% declare themselves post-operatively by: (*a*) profuse and persistent discharge of bile through the abdominal incision; should the external discharge cease, the ominous signs of jaundice and an epigastric swelling are quick to announce the gravity of the case; and (*b*) deepening obstructive jaundice which, in the early phase of convalescence, is often attributed to retained common-duct stone or to the evil effects of blood transfusions.

Some few patients who have sustained some operative injury to the ducts do not display the signs and symptoms of partial or complete blockage until some months or years after cholecystectomy. As fibrosis increases and the channel narrows, the signs of cholangitis and liver damage make a tardy appearance. Repeated intermittent attacks of fever, rigors and jaundice suggest a diagnosis of choledocholithiasis, and in fact such strictures are commonly associated with stone or biliary mud.

The effects of operative strictures of the bile ducts from an economic and social point of view are staggering. The icterus cannot be hidden and prevents normal social intercourse and daily work; the intractable pruritus causes insomnia; rigors, pyrexia, anorexia and a stubborn type of malaise are constant findings; liver damage is progressive and leads to biliary cirrhosis and portal hypertension; and weight loss, due to recurring gastro-intestinal disorders, is marked. On top of all this, it is usual, as I have said, for the patient to have suffered the hopes and disappointments of more than one surgical attempt to restore the flow of bile into the intestines.

Principles of Repair

(1) If the surgeon recognizes that the bile duct has been injured during the course of an operation such as cholecystectomy, he should make every attempt at immediate repair.

(2) If it is at all possible to perform an axial or end-to-end anastomosis and thus preserve the sphincteric mechanism, i.e. by choledochocholedochostomy or by hepaticocholedochostomy, this should be the procedure of choice.

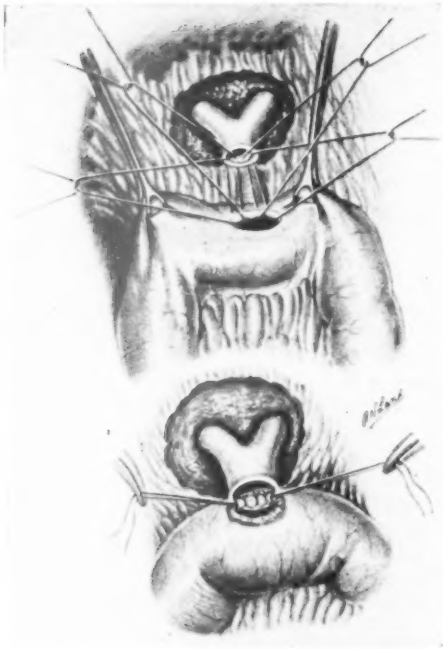

FIG. 1.—Hepaticojejunostomy for stricture of the bile duct. The operation is completed by performing an entero-anastomosis between the afferent and efferent limbs of the proximal jejunum.

(3) If an axial anastomosis is impracticable, the proximal end of the duct should be anastomosed to a loop of the proximal jejunum rather than to the duodenum. When a loop of proximal jejunum is employed, a long entero-anastomosis should be made in order to deflect gastric and intestinal contents away from the biliary-enteric stoma (Fig. 1). Some surgeons prefer the Roux-Y method, but in my opinion this more complicated type of anastomosis should be reserved for those cases in which the mesojejunum is unduly short.

(4) All anastomoses must be made accurately, without tension, and with not more than six interrupted sutures of medium 000 chromic catgut. Mucosa should always be approximated to mucosa.

(5) When an end-to-end ductal union is performed, the suture line should always be splinted by a T-tube. The long or vertical limb of the T-tube must not emerge through the suture line in the duct, but at a point above or below it.

(6) Longmire's operation should not be considered unless an operative cholangiogram shows that the left and right hepatic ducts are in communication. This operation is rarely called for, and in most instances the results from its use are discouraging.

(7) In many cases it is advisable to display the portal vein and hepatic artery (and its branches) before dealing with the duct remnant, which may be extrahepatic, hilar or intrahepatic.

It should be noted that the *coring out of a biliary fistula* and the implantation of such a fistulous tract into the stomach, duodenum or jejunum is doomed to failure, although in a few published cases the immediate results appear to have been good. Bridging the gap or restoration of bile-duct continuity with the aid of vitallium, polyethylene, rubber, silicone or other tubes is an interesting study in bile-duct surgery. Unfortunately, however, all such tubes or prostheses sooner or later become blocked with cholesterol and calcium bilirubinate deposits and have to be withdrawn at a secondary operation. The ideal prosthesis, or an adequate heterogenous or homologous substitute for an injured duct, has not yet been discovered.

Prognosis

The best results are obtained when the initial repair is carried out at the time of the injury or as soon after the injury as possible. With *extrahepatic bile-duct strictures*, good results can be anticipated in some 80% but with *hilar or intrahepatic strictures* the cure-rate rarely exceeds 25%.

Fully one-third of the patients who have undergone bile-duct reconstruction procedures die within a period of four years or so, either from the operation itself or else from the effects of obstruction, i.e. from suppurative cholangitis, biliary cirrhosis, portal hypertension, hepatic coma, &c.

Because of the possibility of an eventual good result, each patient who develops recurrent signs and symptoms of bile-duct stricture should be subjected to yet another attempt to repair it. If patients are symptom-free after four years following bile-duct reconstruction, there is a 90% chance of complete cure.

REFERENCES

ALONSO-LEJ, F., REVER, W. B., Jr., and PESSAGNO, D. J. (1959) *Int. Abstr. Surg.*, **108**, 1.
BEAVAN, T. E. D., and DUNCAN, G. W. (1946) *Brit. J. Surg.*, **33**, 378.
CATTELL, R. B., and BRAASCH, J. W. (1959) *Surg. Gynec. Obstet.*, **109**, 531.
DRAGSTEDT, L. R., and WOODWARD, E. R. (1952) *Surg. Gynec. Obstet.*, **94**, 53.
DURELL, H. L., and HALLIWELL, A. C. (1952) *Lancet*, ii, 1203.
GROSS, R. E. (1953) The Surgery of Infancy and Childhood. Philadelphia.
MAINGOT, R. (1955) *Brit. med. J.*, i, 1256.

BOOKS RECEIVED FOR REVIEW (contd. from p. 532)

Licht (S.), ed. Massage, manipulation and traction. pp. xiii+275. New Haven: Licht. $10.00. 1960.

Liddell (E. G. T.). The discovery of reflexes. pp. vi+174. London: Oxford University Press. 30s. 1960.

MacGregor (A. R.). Pathology of infancy and childhood. pp. viii+631. Edinburgh and London: Livingstone. 75s. 1960.

Maddin (S.), Danto (J. L.), and **Stewart (W. D.).** Basic Office Dermatology. pp. xix+308. Springfield, Ill.: Thomas. Oxford: Blackwell. 94s. 1960.

Markowitz (J.), Archibald (J.), and **Downie (H. G.).** Experimental Surgery. Including surgical physiology. 4th ed. pp. xii+931. London: Baillière. 100s. 1959.

Marshall (J.). Diseases of the Skin. pp. viii+944. Edinburgh and London: Livingstone. 84s. 1960.

Middlemiss (H.). Radiology as a diagnostic aid in clinical surgery. pp. viii+151. London: Heinemann. 30s. 1960.

Mitchell (J. S.). Studies in radiotherapeutics. pp. vii+274. Oxford: Blackwell. 52s. 6d. 1960.

Quiring (D. P.). The extremities. Revised and edited by John H. Warfel, Ph.D. pp. 120. London: Kimpton. 24s. 6d. 1960.

Ramoń y Cajal (S.). Studies on vertebrate neurogenesis. Translated by Lloyd Guth, M.D. pp. xiv+432. Springfield, Ill.: Thomas. Oxford: Blackwell. £5 8s. 1960.

Rhodes (P.). Fluid balance in obstetrics. A critical review. pp. x+169. London: Lloyd-Luke. 25s. 1960.

Rice (E. W.). Principles and methods of clinical chemistry for medical technologists. pp. xvii+286. Springfield, Ill.: Thomas. Oxford: Blackwell. 56s. 1960.

Roberts (F.). An introduction to human blood groups. pp. viii+85. London: Heinemann. 9s. 6d. 1960.

Rose (W.), and **Carless (A.).** Manual of Surgery. 19th ed. Edited by Sir Cecil Wakeley, M. Harmer and S. Taylor. pp. xv+1389. London: Baillière. 84s. 1960.

Sauer (G. C.). Manual of skin diseases. pp. xvii+269. London: Pitman. 70s. 1959.

Schade (R. O. K.). Gastric cytology. Principles, methods and results. pp. viii+83. London: Arnold. 35s. 1960.

Schamroth (L.), and **Segal (F.).** An introduction to congenital heart disease. pp. ix+116. Oxford: Blackwell. 22s. 6d. 1960.

Seward (C.). Bedside diagnosis. 5th ed. pp. xix+479. Edinburgh and London: Livingstone. 25s. 1960.

Sigerist (H. E.). Henry E. Sigerist on the history of medicine. Edited by F. Marti-Ibáñez. pp. xviii+313. New York: MD Publications. $6.75. 1959.

Sigerist (H. E.). Henry E. Sigerist on the sociology of medicine. Edited by M. I. Roemer. pp. xiii+397., New York: MD Publications. $6.75. 1960.

Simon (G.). Principles of bone X-ray diagnosis. pp. xxi+170+8. London: Butterworth. 57s. 6d. 1960.

Smialowski (A.), and **Currie (D. J.).** Photography in medicine. pp. xviii+330. Springfield, Ill.: Thomas. Oxford: Blackwell. £5 16s. 1960.

Sykes (W. S.). Essays on the first hundred years of anæsthesia. Vol. 1. pp. 171. Edinburgh and London: Livingstone. 30s. 1960.

Thomson (W. A. R.), ed. Practical dietetics. pp. 64. London: The Practitioner. 4s. 6d. 1960.

Top (F. H.). Communicable and infectious diseases. Diagnosis, prevention, treatment. 4th ed. pp. 812. St. Louis: Mosby. London: Kimpton. 150s. 1960.

United States Army, Medical Dept. Surgery in World War II. Neurosurgery, Vol. 2. Published in 2 volumes. pp. xxvi+705. Washington, D.C.: Office of the Surgeon General, Dept. of the Army. $7.00. 1959.

Villee (C. A.), ed. The placenta and fetal membranes. pp. x+404. Baltimore: Williams and Wilkins. London: Baillière. 80s. 1960.

Vitalstoffe—zivilisationskrankheiten. A journal of the International Society for Research on Nutrition and Vital Substances. Heft 16 (IV). Hanover: International Society for Research on Nutrition and Vital Substances. 1959.

Weber (F. Parkes). Miscellaneous notes (sixth series). pp. 10. London: Lewis. 3s. 1960.

Williams (L.). Tomorrow will be sober. pp. 207. London: Cassell. 15s. 1960.

Willmer (E. N.). Cytology and evolution. pp. x+430. New York and London: Academic Press. 70s. 1960.

Wohl (M. G.), and **Goodhart (R. S.),** eds. Modern nutrition in health and disease. Dietotherapy. 2nd ed. pp. 1152. London: Kimpton. 138s. 1960.

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Section of Medicine

President—E. R. CULLINAN, M.D.

Meeting
October 27, 1959

Dr. E. R. CULLINAN delivered his Presidential Address entitled **Ulcerative Colitis—The Present Position.**

Meeting
November 24, 1959

A SYMPOSIUM was presented by the Royal Air Force Institute of Aviation Medicine on **Medical Problems of High Speed Travel.** The Symposium was introduced by Air Commodore W. K. STEWART; the opening papers were: **Accelerations.**—Squadron Leader P. HOWARD; **Problems of Kinetic Heating.**—Dr. D. MCK. KERSLAKE; **Man's Pressure Environment.**—Wing Commander P. D. G. V. WHITTINGHAM; **Review of Cosmic Radiation Effect in Flight.**—Wing Commander F. LATHAM.

Meeting
February 2, 1960

A JOINT MEETING was held with the Section of Pathology when there was a discussion on **The Pathologist and the Patient** opened by Professor ALAN KEKWICK, Professor J. W. S. BLACKLOCK and Dr. R. R. WILSON.

Dr. E. R. CULLINAN (President of the Section of Medicine) was in the Chair.

Meeting
February 23, 1960

BACTERIAL ENDOCARDITIS

Dr. Graham Hayward (London):

Diagnosis of Bacterial Endocarditis

Diagnosis in the classical case is based on the presence of fever in a patient with heart disease, splenomegaly and arterial emboli, and is confirmed by a positive blood culture. In pre-antibiotic days there was no urgency in diagnosis as there was no effective treatment and in the fully developed case the diagnosis was usually easy. Now, although antibiotic control of the infecting organism is usually possible, early mortality is still as high as 27%. One of the factors responsible is the delay in diagnosis, usually more than one month from the onset of symptoms and sometimes as long as six months. The difficulty in early diagnosis is caused partly by the insidious onset of the disease, by failure to think of bacterial endocarditis when the clinical picture does not conform to the classical textbook description, and by failure to realize that this disease is not just confined to the younger age groups. Dormer (1958) has shown by analysis of the Registrar-General's reports that the number of deaths from bacterial endocarditis in patients over the age of 50 is the same now as in 1939 when no treatment was available.

In my series of 112 cases (Table I) the types of underlying heart disease are in general agreement with other published series and show the dominance of rheumatic heart disease. The commonest rheumatic lesion is mitral incompetence and bacterial endocarditis is rare in pure mitral stenosis. In elderly patients the predominance of underlying mitral incompetence is even more marked and many of these patients have been known to have loud mitral systolic murmurs for years with no symptoms or signs of heart failure.

TABLE I.—BACTERIAL ENDOCARDITIS

Total cases	112		(male 75, female 37)
Rheumatic	86		
Congenital	19		
Arteriosclerotic	4		
Syphilitic	3		
Positive blood culture	81		(72%)
Negative blood culture	31		(28%)
Total early mortality	30	(27%)	+ve culture 18 (23%)
			−ve culture 12 (38%)
Cause of death:			
Uncontrolled infection	60%		
Congestive failure	27%		
Embolism	13%		

The group of cases of congenital heart disease, although small, is of interest as prognosis is best in this group and recovery occurs if antibiotic cure of the infection is possible. The commonest variety of congenital heart disease to be infected is a ventricular septal defect. Bacterial endocarditis is said not to occur in atrial septal defect but this applies only to the secundum type

of defect. This series includes 3 cases of bacterial endocarditis with an ostium primum defect.

One reason for advising ligation of a patent ductus arteriosus is to prevent the later occurrence of bacterial endocarditis. However, infection may take place on a congenital aortic valve lesion in association with a patent ductus. Here the diagnosis is difficult or impossible in the presence of the machinery murmur but the persistence of an ejection type systolic murmur after ligation of the duct is often due to associated aortic disease. For this reason penicillin cover should still be given for dental extractions even after ligation of a patent duct.

Bacterial endocarditis is generally thought not to occur in cyanotic congenital heart disease, but in 3 of the present series the patients were cyanosed (2 with the tetralogy of Fallot and 1 with pulmonary stenosis and an atrial septal defect).

Heart murmurs have been present in all cases by the time the disease was established. In the majority of cases heart disease had previously been diagnosed. In some, systolic murmurs had been considered innocent and the phonocardiogram of one such patient is published in a standard textbook as a typical example of the innocent apical systolic murmur. Another example is a patient with subaortic stenosis in whom a basal ejection type murmur had been thought to be insignificant. In some cases the heart had previously been considered normal; in these the infection is often superimposed on a bicuspid aortic valve with the appearance of signs of aortic incompetence. Less commonly the infection may have affected a minimal abnormality of the mitral valve, as shown later by the development of typical signs of mitral incompetence.

A definite precipitating cause for the infection is rarely found but there is sometimes a history of recent dental extractions or uterine infection. Operations on the prostate or rectum may cause bacterial endocarditis in the elderly, usually with a highly resistant enterococcus. Infection may follow cardiac surgery, particularly on the mitral valve, the infecting organism usually being a staphylococcus. Here the illness runs an acute course and the diagnosis is easily made.

Clinical diagnosis is made earliest in those cases where the symptoms indicate the presence of fever, although frequently the disease is suspected only when fever recurs after the indiscriminate use of short courses of antibiotics. More commonly the onset is insidious with vague general symptoms such as malaise, and the presence of a low-grade pyrexia is unsuspected; in this group diagnosis is often delayed for months. Fever is usually but not necessarily persistent in the untreated case and afebrile periods do occur.

Embolic episodes may occur early with the presenting symptom a major arterial embolism, e.g. in the brain, spleen or limbs. Minor embolic symptoms are common, such as the occurrence of painful sites in the finger or toe, or sudden, relatively short-lasting pains in other parts of the body. The significance of these symptoms is often realized only in retrospect.

Diagnosis is particularly difficult when the symptoms are attributed to active rheumatism, disease of the central nervous system or renal failure. Arthralgia is common in bacterial endocarditis but in some cases there is pain, redness and swelling of one or several joints, and this in association with fever and the presence of a heart lesion naturally leads to a diagnosis of acute rheumatism. Clinically the differential diagnosis is difficult and, in the absence of embolic signs, clubbing, splenomegaly or microscopic hæmaturia, may be impossible. In bacterial endocarditis the fever and arthritis will not respond dramatically to the administration of salicylates and if these signs persist blood cultures should be taken immediately. If steroids are given to treat the supposed rheumatic fever the results may be disastrous. In 3 such cases, fever and joint pains subsided quickly with marked subjective improvement. However, in 2 cases after seven and ten days' treatment, multiple arterial emboli occurred, the signs of mitral incompetence became more marked and death followed in a few days. At autopsy there was gross disorganization of the mitral valves with rupture of a cusp and chordæ tendinæ. In the third case satisfactory progress seemed to be made but gross clubbing of the fingers appeared in a few weeks, and although there was no further pyrexia, blood cultures yielded a heavy growth of *Streptococcus viridans*.

Symptoms suggesting involvement of the central nervous system are common in bacterial endocarditis. If the endocarditis is caused by a pyogenic organism a cerebral abscess or meningitis may occur but in these cases the patient is acutely ill and the diagnosis readily made. In subacute bacterial endocarditis neurological symptoms may occur in the absence of the more obvious clinical manifestations of the disease and this group provides a large number of cases in which the diagnosis is missed or greatly delayed. It is common for the early symptoms to be regarded as psychoneurotic and many of these patients have been under psychiatric treatment. In some cases there are frank psychotic symptoms or symptoms thought to be

due to cerebral arteriosclerosis in the elderly. In these cases there are often signs of mild congestive heart failure and fever is ascribed to pulmonary infection or infarction.

The second group of neurological symptoms are those due to a cerebral embolism which may be the first symptom of the disease, causing a transient or persistent hemiplegia, monoplegia or loss of vision.

In the third group symptoms and signs may suggest the presence of a space-occupying lesion with severe headaches, mental confusion and bilateral papillœdema.

In the presence of psychoneurotic symptoms or clinical manifestations suggesting organic disease of the brain in a patient of any age with valvular heart disease bacterial endocarditis should always be considered. Careful temperature records will usually show some degree of pyrexia and clinical examination will often elicit such signs as petechiæ, splenomegaly or clubbing.

The occurrence of unexplained fever in any patient with valvular heart disease should always lead to a presumptive diagnosis of bacterial endocarditis. The frequency of atypical modes of onset of this disease should be remembered. Short afebrile periods are not uncommon in the early stages of the disease and even a short course of any of the commonly used antibiotics may render the patient afebrile for several weeks. Measurement of the blood sedimentation rate provides a useful screening test as it is almost always raised, even in the absence of fever. Similarly microscopic examination of the urine will nearly always show an increased number of red cells.

The final proof of the diagnosis is made by recovering the infecting organism from the blood stream. Every effort should be made to get a positive blood culture as treatment can only be effectively planned if the nature of the infecting organism is known and its sensitivity to various antibiotics determined. Uncontrolled infection is still the commonest cause of death in bacterial endocarditis—60% in the present series.

Bacteriæmia in the untreated case of bacterial endocarditis tends to be persistent rather than intermittent and thus a positive blood culture is usually obtained in the first blood sample to be examined. Although multiple blood cultures are frequently taken, it is exceptional for the later specimens to be positive if the earlier ones were negative. It is our practice to take 3 blood cultures in the first forty-eight hours, the specimens being taken without reference to the patient's temperature, and then to institute initial treatment with penicillin. Subsequent treatment is planned when the results of the bacteriological investigations are available and the sensitivity of the organism to antibiotics, either singly or in combination, is known. Laboratory tests should show which antibiotics will kill the organism as distinct from inhibiting its growth and if treatment is planned accordingly there is a remarkably close correlation between the clinical response to treatment and the bacteriological assessment of sensitivity. A first-class bacteriological screen is necessary if bacterial endocarditis is to be adequately treated and I am indebted to Professor L. P. Garrod and Dr. R. A. Shooter at St. Bartholomew's Hospital and to Dr. R. E. B. Hudson at the National Heart Hospital for their help.

In 28% of cases in the present series repeated blood cultures were negative although the other clinical criteria for the diagnosis were present. In cases of congenital heart disease with a left-to-right shunt many authors have reported difficulty in getting positive blood cultures, but this has not been encountered in the present series. This group of bacteriologically negative cases is a difficult one and the mortality is significantly higher than in the cases where blood cultures were positive. Although in the absence of a positive blood culture the diagnosis is always somewhat uncertain, there should be no hesitation in treating these patients energetically if no other cause for the pyrexia can be found. In these cases it is our practice to assume that infection has been caused by a resistant organism and to start treatment with penicillin in high dosage (10–20 mega units daily), adding streptomycin after one week if the pyrexia does not respond. Even if response to a full course of treatment is satisfactory, the relapse rate is high and the disease often runs a prolonged course, sometimes for two to three years with recurrent remissions and relapses. In a high proportion of patients in this group there is evidence of aortic stenosis and the course is characterized by recurrent episodes of arterial embolism and fever. One such patient was treated in five London teaching hospitals for relapsing bacterial endocarditis and over a period of three years more than 100 blood cultures were negative, yet at autopsy the typical vegetations of bacterial endocarditis were found in the aortic valve and section of the vegetations showed apparent bacterial colonies deeply buried in the base.

It has been suggested that this group of bacteriologically negative cases includes many examples of the "collagen diseases" such as lupus erythematosus with Libman-Sachs endocarditis. Lupus erythematosus and bacterial

endocarditis have many features in common, such as fever, arthralgia, hæmaturia, raised sedimentation rate and increased gamma globulin, but in lupus erythematosus the cardiac manifestations are unimpressive until late in the disease and embolic signs are absent. In case of doubt antibiotics should always be tried, either penicillin alone or with streptomycin, before steroids are used.

Summary.—Bacterial endocarditis is difficult to diagnose in its early stages and the symptoms may suggest disease of any system in the body. If, however, the diagnosis is considered in every patient with heart disease with unexplained pyrexia fewer errors will be made. Cardiac murmurs are frequent in febrile and anæmic patients and their significance may require expert assessment. Experience with this disease over the past fifteen years has shown that in young patients the chief differential diagnosis is from active rheumatic infection. In older patients the disease is often not considered and its manifestations are thought to be due to the presence of an occult carcinoma as a cause for anæmia and pyrexia, diseases of the central nervous system or renal failure. Although the chief cause of death is failure to control the infection, early diagnosis should help to lessen the frequency of congestive failure and embolism and may make the organism more accessible to antibiotics.

REFERENCE

DORMER, A. E. (1958) *Brit. med. J.*, i, 63.

Dr. Mary Barber (London):

Bacteriological Aspects:

Mechanism and source of infection.—Acute endocarditis may occur as a secondary phenomenon in almost any form of septicæmia, but primary infection of the heart valves, or subacute bacterial endocarditis, is usually caused by bacteria which form part of the normal flora of the human body. In the vast majority of cases, subacute bacterial endocarditis is due to infection of a previously damaged or congenitally abnormal heart valve by *Strep. viridans* normally present in the mouth. Transient invasion of the blood stream with these organisms is so frequent that Lewis and Grant (1923) regarded it as "almost physiological". For the most part the cocci are rapidly phagocytosed, but according to McNeal *et al.* (1944), the endothelium covering the valves is less bactericidal than that elsewhere and may, therefore, become damaged by the ingested cocci. The damaged area is then liable to be covered by a deposit of fibrin which protects the streptococci and permits their multiplication.

It follows that any manipulation likely to cause bacteriæmia is potentially dangerous for anyone with abnormal heart valves. Okell and Elliott (1935) first drew attention to the frequency of transient bacteriæmia following dental extraction, particularly if the gums are unhealthy. They took blood cultures within a few minutes of tooth extraction and isolated streptococci from 72 of 100 patients with gum disease and 12 of 38 patients with apparently healthy gums. Rocking of teeth without extraction (Okell and Elliott, 1935) or massage of gums (Richards, 1932) may also send streptococci into the blood stream, and Round *et al.* (1936) isolated *Strep. viridans* from 1 of 10 blood cultures taken after chewing mint lumps. Bacteriæmia has been recorded after operative manipulation of many other sites, but only tonsillectomy approaches dental extraction in showering *Strep. viridans* into the blood stream (Elliott, 1939).

Dowling *et al.* (1952) recorded an increasing incidence of staphylococcal endocarditis, and drew attention to the intravenous injection of narcotics as a possible source of infection. Of 25 cases studied by them, 11 (6 inpatients under 30) were heroin addicts. Staphylococcal endocarditis, often due to coagulase-negative strains, is a serious complication of cardiac surgery (Resnekov, 1959).

Bacteria responsible for endocarditis.—Until the introduction of penicillin and other antibiotics about two-thirds of all recorded cases of endocarditis were due to *Strep. viridans*. Other forms of streptococci, pneumococci and staphylococci (coagulase-positive and -negative strains) accounted for most of the remaining cases. Table I gives the incidence of various species in 1,000 cases, analysed from a large number of sources by Perry (1936), and also mentions some of the other bacteria, which have occasionally been recorded as the ætiological agent.

TABLE I.—BACTERIOLOGY OF BACTERIAL ENDOCARDITIS

	Percentage Incidence (Perry, 1936)
Streptococci	68
Staphylococci	10
Pneumococci	11
N. gonorrhœæ	4·6
Hæmophilus	2·6

N. meningitidis (*see* Perry, 1936)
Bact. coli and other coliform bacilli (*see* Perry, 1936)
Ps. pyocyanea (*see* Perry, 1936)
Brucella (*see* Perry, 1936)
B. anthracis (Thayer, 1931)
Chromobact. prodigiosum (Hawe and Hughes, 1954)
Erysipelothrix rhusiopathiæ (Russell and Lamb, 1940)
Rickettsia burneti (Robson and Shimmin, 1959; Andrews and Marmion, 1959)

Since the clinical use of antibiotics, the incidence of cases due to *Strep. viridans* is still high, but an increasing number due to other bacteria are being recorded. Moreover, since a proportion of the patients with endocarditis due to

Strep. viridans are cured by penicillin, the incidence of this organism among fatal cases has dropped considerably. Table II analyses the

TABLE II.—BACTERIOLOGY OF FATAL CASES OF ENDOCARDITIS OCCURRING IN A SINGLE LONDON HOSPITAL

	1935–1943	1944–1958	Total 1935–1958
Strep. viridans	17 (61%)	13 (35%)	30
Strep. hæmolyticus	—	3	3
Staphylococci	5 (18%)	8 (21%)	13
Pneumococci	1	2	3
H. parainfluenzæ	1	1	2
Enterococci	—	3	3
Micrococci	—	2	2
Ps. pyocyanea	—	2	2
Unidentified cocci	4	4	8
	28	38	66

bacteriology of cases of endocarditis from the post-mortem records of a single London hospital, before and after January 1944 when penicillin was first used in the hospital. It will be seen that in the post-penicillin period the incidence of cases due to *Strep. viridans* had fallen from 61% to 35% and that a much wider variety of bacteria were isolated from the remaining patients than had been the case in the pre-penicillin period.

Incidence and age of fatal cases.—Further analysis of these post-mortem records showed that the incidence of deaths from endocarditis in the hospital fell sharply immediately after the introduction of penicillin and streptomycin and then steadily rose to about the same level as before (Fig. 1). The rise was due to endocar-

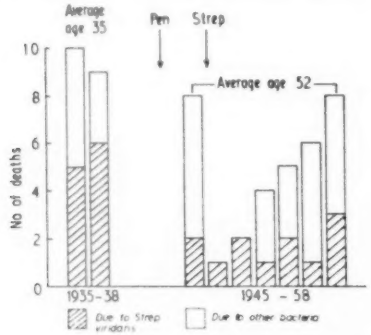

FIG. 1.—Deaths from endocarditis (Hammersmith Hospital): biannual incidence.

ditis caused by bacteria other than *Strep. viridans*. Moreover the average age of the fatal cases in the pre-penicillin period was 35 years and in the post-penicillin period 52 years.

The incidence of deaths from endocarditis occurring at various ages taken from the Registrar-General's returns for England and Wales (*see* Fig. 2) shows a similar shift in age incidence between 1937 and 1957. The total number of cases recorded in 1957, however, is very much

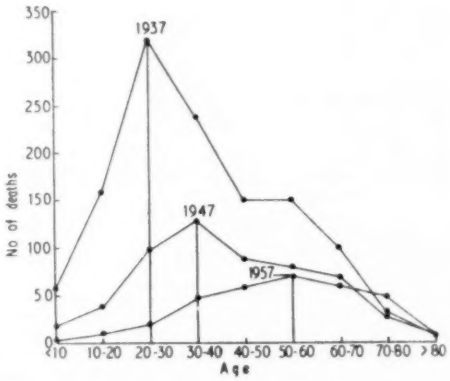

FIG. 2.—Deaths from acute and subacute endocarditis at various ages. England and Wales.

lower than that recorded in 1937. This difference between the Registrar-General's figures for England and Wales and those in a single London hospital is probably partly accounted for by the fact that in a number of the cases included in the latter series the endocarditis was a terminal event and might not have been recorded in the absence of a post-mortem.

Conclusion.—Bacterial endocarditis remains a serious disease with a high mortality. Since the introduction of antibiotics the mortality has been considerably reduced, particularly in younger patients. *Strep. viridans* remains the commonest bacteriological agent, but an increasing number of cases due to other bacteria, many of which are resistant to antibiotics, are now appearing.

REFERENCES

ANDREWS, P. S., and MARMION, B. P. (1959) *Brit. med. J.*, ii, 983.

DOWLING, H. F., LEPPER, M., CALDWELL, E. R., and SPIES, H. W. (1952) *Medicine, Baltimore*, **31**, 155.

ELLIOTT, S. D. (1939) *Lancet*, ii, 589.

HAWE, A. J., and HUGHES, M. H. (1954) *Brit. med. J.*, i, 968.

LEWIS, T., and GRANT, R. T. (1923) *Heart*, **10**, 21.

MCNEAL, W. J., SPENCE, M. J., and SLAVKIN, A. E. (1944) *Amer. J. Path.*, **20**, 95.

OKELL, C. C., and ELLIOTT, S. D. (1935) *Lancet*, ii, 869.

PERRY, C. B. (1936) Bacterial Endocarditis. Bristol.

RESNEKOV, L. (1959) *Lancet*, ii, 597.

RICHARDS, J. H. (1932) *J. Amer. med. Ass.*, **99**, 1496.

ROBSON, A. D., and SHIMMIN, C. D. G. L. (1959) *Brit. med. J.*, ii, 980.

ROUND, H., KIRKPATRICK, H. J. R., and HAILS, C. G. (1936) *Proc. R. Soc. Med.*, **29**, 1552.

RUSSELL, W. D., and LAMB, M. E. (1940) *J. Amer. med. Ass.*, **114**, 1045.

THAYER, W. S. (1931) *Edinb. med. J.*, **38**, 237, 307.

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Management of Bacterial Endocarditis: Treatment and Prognosis

The introduction of antibiotics has dramatically changed the prognosis of bacterial endocarditis, but there are still no grounds for complacency. Fig. 1 shows the death-rate from

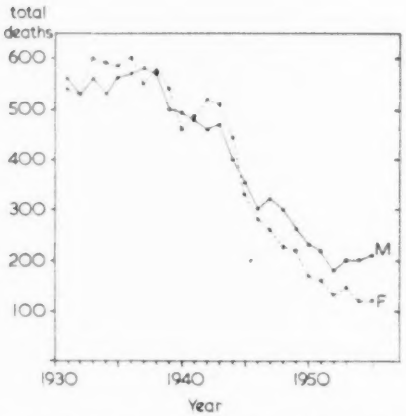

FIG. 1.—Yearly total deaths in England and Wales due to bacterial endocarditis. 9% of all deaths from heart disease (Clawson, 1948). Redrawn from Dormer (1958).

bacterial endocarditis in England and Wales (Dormer, 1958). Although the infection can be controlled in 90–95% of patients, there is still a mortality of up to 30%.

Prophylactic treatment.—It is important to know the cardiac lesions are particularly prone to infection. Acute endocarditis may occur with any septicæmia and attack a previously normal heart. The subacute variety, however, nearly always involves a previously damaged heart. In congenital heart disease patent ductus arteriosus, ventricular septal defect, and bicuspid aortic valve are particularly prone to subacute infection. Pulmonary stenosis and coarctation of the aorta may also be infected, but less frequently. Atrial septal defect very rarely becomes infected unless it is of the ostium primum type. Infective endocarditis in infants is extremely rare.

In acquired heart disease the commonest abnormality to become infected is a mild degree of mitral incompetence or aortic stenosis. Severe and multiple valve lesions are much less commonly involved. Perhaps for this reason bacterial endocarditis is often not considered in patients with obscure fever, the evidence of underlying heart disease being slight or trivial.

Infection usually follows minor surgery, especially dental extraction. Bacterial endocarditis may follow urological procedures such as cystoscopy or prostatectomy, or can occur after childbirth. Much can be done to prevent bacterial endocarditis if antibiotic prophylaxis is given for dental extraction in patients with a known cardiac lesion. After the extraction of a tooth bacteria from the socket (usually *Strep. viridans*) are liberated into the blood stream and may settle upon an already abnormal heart. The importance of dental extraction as a cause has been shown by Hobson and Juel-Jensen (1956) who studied 43 patients with endocarditis due to infection with *Strep. viridans*. In seven patients the attack was definitely related to tooth extraction. Five patients who had some remaining teeth relapsed after treatment, but no relapses occurred in those in whom total extraction had been carried out. It is vitally important that patients with heart disease should have their teeth well cared for and that a patient who has had bacterial endocarditis should have all carious or damaged teeth removed under full antibiotic cover. No septic teeth should be allowed to remain and there should be no hesitation in recommending full dental clearance if in doubt. In a series of 39 cases from Hammersmith Hospital, tooth extraction could be blamed in 9 and antibiotic cover was probably inadequate in 3. Antibiotic cover should consist of 600,000 to 1,000,000 units of penicillin daily for two days before, during, and two days after the extraction, the penicillin being given by injection. Cystoscopy and prostatectomy should always be covered routinely with chemotherapy, for Toh and Ball (1959) have shown that *Strep. fæcalis* endocarditis can occur even in previously normal hearts. Childbirth should always be covered by penicillin in patients with known cardiac disease.

Treatment of subacute bacterial endocarditis.—The antibiotic to be used depends on the infecting organism and its sensitivity, and also to some extent on the accessibility of the lesion. Penicillin may be used as the sole antibiotic only if the organism is highly sensitive, such as a *Strep. viridans* with a sensitivity to penicillin of 0·1 unit/ml. Penicillin alone should be continued only if there is an immediate and full response to treatment and no relapse occurs. Usually it is unwise to administer one antibiotic alone for long periods (*Brit. med. J.*, 1960). Penicillin plus streptomycin is most effective for the treatment of infective endocarditis (Christie, 1953; Finland, 1958) and this combination should be used if the organism is a less sensitive *Strep. viridans* with a sensitivity of perhaps 1–2 units/ml, and in all cases in which positive blood cultures have not been obtained.

In using streptomycin for long periods, careful watch must be kept for ototoxicity or other reactions: this is particularly important in patients with pre-existing renal disease or who develop nephritis as a result of their subacute bacterial infection. In patients over the age of 60, the liability to ototoxicity is greater and half the dose of streptomycin should be administered. Blood levels of streptomycin should not be allowed to rise higher than 20 μg/ml.

Penicillin should be given in a dosage of not less than 2 mega units per day and should be given by injection not less frequently than six-hourly. 39 cases of bacterial endocarditis treated at Hammersmith Hospital received from 2·5 to 12 mega units daily. Penicillin may be given by mouth to supplement injections and reduce their frequency if they become too painful, but the oral route should not usually be used as the sole method of administration. Oral penicillin has been reported as unsatisfactory because of erratic blood levels and gastro-intestinal disturbance by Santos-Buch *et al.* (1957) and by Finland (1958), although Geraci (1958) claimed satisfactory results in 12 patients with 4–6 mega units of phenoxymethyl penicillin combined with streptomycin and probenecid for two weeks. It is essential to maintain a consistently high blood level of penicillin. According to Eagle *et al.* (1953) levels considerably in excess of the concentration necessary to inhibit the organism *in vitro* are required for successful treatment.

Streptomycin should be given in doses of 1 g daily, except in patients over 60 years when the dose should be halved.

The duration of treatment should be from six to twelve weeks, usually eight weeks. At least eight weeks' treatment should be given to patients with negative blood cultures. However, short courses of up to a fortnight have been given with some success and this method is worth considering in patients who cannot be given a protracted course of treatment. Table I shows that in four series comprising a total of 94 patients, the results were on the whole satisfactory, but a short course should only be considered in patients with a highly sensitive organism and immediate response. The type of lesion which is infected also has some bearing on the duration of treatment. For example, infection of a patent ductus arteriosus or ventricular septal defect is very unlikely to increase cardiac damage, whereas infection of a previously damaged aortic valve may result in fatal or extremely serious aortic incompetence, even though the infection has been cured.

TABLE I.—SHORT-COURSE TREATMENT FOR SUBACUTE BACTERIAL ENDOCARDITIS

No. of cases	No. cured	Penicillin mega units daily	Streptomycin grams daily	Reference
12	10 (infection cured in 12)	15–16	0	Hamburger and Stein (1952)
23	18	2	2 (Dihydro-strep.)	Geraci and Martin (1953)
23	20	2	2 (Dimycin)	Geraci (1955)
36	28 (infection cured in 36)	2 (+ pro-benecid)	2 (Dimycin)	Geraci (1958)
Total 94	76 (80%)	—	—	—

Adjuvants to penicillin.—Since penicillin is excreted by the renal tubules, substances which block this tubular excretion may be expected to enhance the blood level, and thus potentiate the effect of penicillin (Stuart-Harris *et al.*, 1949). The most satisfactory adjuvant is probenecid, which may be given in a dosage of 0·5 g four times daily. It is usually well tolerated, but occasionally gives rise to nausea and dyspepsia. Its use should always be considered when large doses of penicillin do not apparently produce a complete response in a patient with a sensitive organism or in a patient in whom the organism has not been isolated, and penicillin is being used "blind". Corticosteroids have been suggested as possible adjuvants to minimize fibrosis of valves and damage to the myocardium, but according to Finland (1954) their use is inadvisable, as is the use of anticoagulants, which may give rise to hæmorrhage (Finland, 1954; Priest *et al.*, 1946).

Antibiotics other than penicillin and streptomycin.—Tetracycline is occasionally advocated but in general is a poor drug for the treatment of infective endocarditis because it is bacteriostatic rather than bactericidal. It should never be used alone, but always in combination with another antibiotic, preferably a bactericidal one. It is useful in a patient who, receiving penicillin and streptomycin, becomes intolerant of streptomycin. If tetracycline is given over a long period, vitamin B_1 supplements should be added to reduce the risk of sore tongue or staphylococcal intestinal infection. Chloramphenicol should rarely be used because of the dangers of bone-marrow damage when long courses and high doses are used. It should only be considered if it is the only suitable antibiotic in a desperately ill patient.

Other drugs which may be used are: erythromycin (Geraci and Martin, 1954), novobiocin, bacitracin, neomycin, vancomycin (Geraci *et al.*, 1958), and polymyxin (Finland, 1958). Erythromycin is useful for penicillin-resistant staphylococcal infections, but should never be used alone

owing to the danger of bacterial resistance. It may be combined with novobiocin in a dosage of 1–2 g per day of each drug. This combination can, however, produce toxic rashes. Neomycin and vancomycin are toxic drugs which carry the risk of damage to the VIII nerve and to the kidneys, and should only be used if absolutely essential.

Although the commonest organism in bacterial endocarditis is the *Strep. viridans*, infection may occur with a *Strep. fæcalis*, staphylococcus, or occasionally with Gram-negative organisms. *Strep. fæcalis* endocarditis should be treated as for a moderately sensitive *Strep. viridans* infection with penicillin 10–20 mega units daily, probenecid, and streptomycin. Staphylococcal endocarditis should be treated in the same way if the staphylococcus is sensitive to penicillin and streptomycin. If not, the best combination is probably erythromycin and novobiocin, possibly with streptomycin also if the organism is sensitive to this drug.

Dormer (1959) has listed suggestions for antibiotics for use with less common Gram-negative infections:

Organism	Antibiotic
Brucella	Tetracycline + streptomycin
Hæmophilus influenzæ	Streptomycin + chloramphenicol + tetracycline or penicillin and streptomycin
Salmonella	Chloramphenicol
Pseudomonas	Polymyxin + tetracycline + streptomycin or neomycin
Bacillus coli	Streptomycin + tetracycline
Gonococcal infections	Penicillin

Two new antibiotics have been commented on by Dormer (1959) in his review. Ristocetin is active against Gram-positive organisms including staphylococci, but must be given intravenously. It is bactericidal, and preliminary studies have shown no development of resistance or cross-resistance. Toxicity consists of neutropenia, thrombocytopenia, thrombophlebitis, fever, and rashes; the frequency of these reactions depends directly upon the dose used. Vancomycin is a potent antibiotic against the staphylococcus but tends to accumulate and may cause renal damage as well as ototoxicity. When renal impairment is present serum levels may be necessary to control the dose (Dutton and Elmes, 1959).

Surgical treatment.—Infection at the site of an arteriovenous communication, such as a patent ductus arteriosus, may be cured by closure of the fistula. Needless to say, in a patient with an infected ductus, the infection should be thoroughly treated, and then the ductus ligated. Now that closure of a ventricular septal defect is a practicable procedure at low risk, the same principles should apply. Coarctation of the aorta, when infected, will also require resection on these as well as other grounds. It should be remembered, however, that a number of patients who have infective endocarditis with coarctation of the aorta have the infection on a bicuspid aortic valve.

Finally, in some cases a splenic infarct may become infected, and splenectomy can cure the infection. This complication should be kept in mind in patients with persistent fever, bacteriæmia, and pain and tenderness in the left hypochondrium. A left pleural effusion may occur also (Lingeman *et al.*, 1956).

Results of treatment of subacute bacterial endocarditis.—The infection is usually controlled in 90–95% of patients if the patient is alive after two weeks' treatment (Friedberg, 1956). The mortality, however, is higher than this figure would suggest, being from 25–45% (Cates and Christie, 1951; Friedberg, 1956; Jones *et al.*, 1947). Morgan and Bland (1959) reported that 21% of 119 patients died during a ten-year follow-up period. It is well known that although the infection may be cured, the patient may still die from irreversible cardiac failure, produced by progressive myocardial damage or by gross endocardial destruction such as rupture of an aortic valve cusp. In the Hammersmith series of 30 patients only 11 died, the infection being cured in all but 4. Thus 7 patients died of cardiac damage despite cure of the infection (Table II).

TABLE II.—RESULTS OF TREATMENT OF BACTERIAL ENDOCARDITIS (HAMMERSMITH HOSPITAL)

	Acute		*Subacute*	
Total cases	9		30	
Infection cured—alive	2	(22%)	19	(63%)
Died infected	5		4	
Infection cured but died of heart failure, ruptured valve or emboli	2	(78%)	7	(37%)
Previous cardiac lesion				
Aortic valve disease	2		8	
Mitral valve disease	1 (post op.)		6	
Combined mitral and aortic	1		6	
Ventricular septal defect	1 (post op.)		2	
Patent ductus arteriosus	0		0	
Pulmonary stenosis	0		1	
Coarctation	0		3	2 with aortic incompetence
Other heart disease	0		2	
Nil	4		2	

The commonest condition to be infected was aortic valve disease, often combined with mitral valve disease, and the mortality was particularly high in these conditions. The relationship of mortality to the infecting organism is shown in Table III. *Strep. viridans* was the most frequent organism responsible in all cases, including the fatal ones. Both the patients infected with a hæmolytic streptococcus died, as did 3 out of 4 infected with *Staph. pyogenes*. In 10 cases the diagnosis was made clinically, repeated blood

TABLE III.—BLOOD CULTURES AND MORTALITY (HAMMERSMITH HOSPITAL)

Organisms	No. of patients with acute infection	No. of patients with subacute infection	Deaths
Strep. viridans	0	11	7
"Non-hæmolytic" streptococcus	0	3	0
Hæmolytic streptococcus	1	1	2
Strep. faecalis	1	1	2
Staph. pyogenes	4	0	3
Staph. albus	1	1	0
Bacillus coli	0	1	0
Pyocyaneus	2	0	2
Uncertain (Vegetations sterile. Blood cultures equivocal)	0	2	2
Total patients	9	20	18

cultures being negative. Aortic incompetence is a particularly sinister lesion in this respect, since many cases develop greater incompetence afterwards which leads to irreversible congestive heart failure. Perforation of a valve cusp may occur (Berger and Kossmann, 1951; Morgan and Bland, 1959). An aneurysm of the valve cusp may occur. Saphir and Leroy in 1948 reported aneurysms of the valves in 5 of 12 patients suffering from infective endocarditis between the years 1943 and 1946. However, in 45 patients who suffered from the disease between 1935 and 1943, no valve aneurysms were found. These workers attributed the aneurysms of the valve cusps to healing as a result of chemotherapy. Mycotic aneurysms as a result of infected emboli may also prove fatal (Cates and Christie, 1951), as may emboli to various sites, particularly coronary and cerebral.

Renal insufficiency may be a cause of death. Morgan and Bland (1959) reported an incidence of 4% in their early cases. In an analysis of 52 cases, Newman *et al.* (1954) noted that 8 patients died with evidence of renal insufficiency: in none of these had the infection been cured. The renal lesions consisted of focal embolic glomerulonephritis, diffuse glomerulonephritis and multiple renal infarcts. It is less likely that patients in whom the infection has been cured will die of renal insufficiency.

Evidence of accompanying rheumatic myocarditis was found by Cates and Christie (1951) and a case of the solitary myocardial abscess in subacute bacterial endocarditis has been reported by Berger and Kossmann (1951). Saphir *et al.* (1950) have emphasized the importance of myocardial lesions in bacterial endocarditis. These include focal and diffuse myocarditis, microabscesses, perivascular cellular infiltration and multiple minute areas of infarction.

Factors contributing to poor results.—These factors require careful analysis in view of the appreciable mortality in this condition. Jones *et al.* (1947) showed that late diagnosis was a potent cause of failure, presumably because the infection had produced irretrievable cardiac damage. Cates and Christie (1951) found that only 36% of patients with recent infection died as compared with 63% of those with infection of more than twenty weeks' duration before the start of treatment. Priest *et al.* (1947) found that the average duration before treatment of the disease was 9·2 weeks in the patients who were ultimately cured, but was 22·5 weeks in those in whom the disease proved fatal. It is clear therefore that early diagnosis is vital. Poor or inadequate chemotherapy which fails to sterilize the infection is also an important cause of failure.

Cates and Christie (1951) found that poor nutrition was a very bad prognostic sign, 70% of badly nourished patients dying.

Heart failure at the start of treatment, or recurring during treatment, is a very bad prognostic omen. Newman *et al.* (1954) reported that 28 of 34 cases with congestive heart failure died, although in 11 of these the treatment had been inadequate. They showed, that even though the infection was cured, 33% of patients with heart failure died within two years. The type of cardiac lesion infected has a definite bearing on the prognosis. Conditions which are not made worse by the infection, such as patent ductus arteriosus, ventricular septal defect, and coarctation of the aorta, are not likely to be followed by further cardiac disorder.

The importance of irreversible cardiac damage, even though the infection has been cured, is shown in Figs. 2 and 3. Fig. 2 shows the temperature chart of a patient in whom the infection was cured. Despite this, however, the patient died subsequently of intractable congestive heart failure, and at necropsy was found to have a ruptured aortic cusp. Fig. 3 shows a very similar temperature chart from a patient with an infected ventricular septal defect. The organism was *Strep. viridans*. The patient made a complete recovery because the infection had not increased the cardiac damage. Treatment was more intensive in the second case, and it is perhaps arguable that rupture of the aortic cusp due to the infection might have been avoided if streptomycin had been given in addition to penicillin in the first case. Long-term prognosis in the survivors of bacterial endocarditis has been analysed by Morgan and Bland (1959). Of 119 patients who survived bacterial endocarditis, 42 were ultimately in congestive heart failure.

Finally, age is important. Cates and Christie (1951) found that the mortality was 30% in patients under 25 years, but 54% over the age of 50.

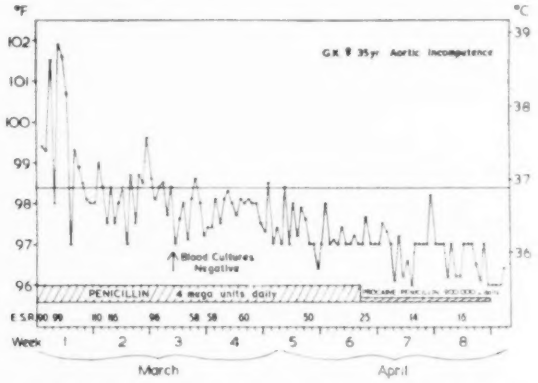

FIG. 2.—Temperature chart and relevant data in a patient with aortic incompetence in whom the infection was cured, but rupture of an aortic valve cusp led to death from congestive heart failure.

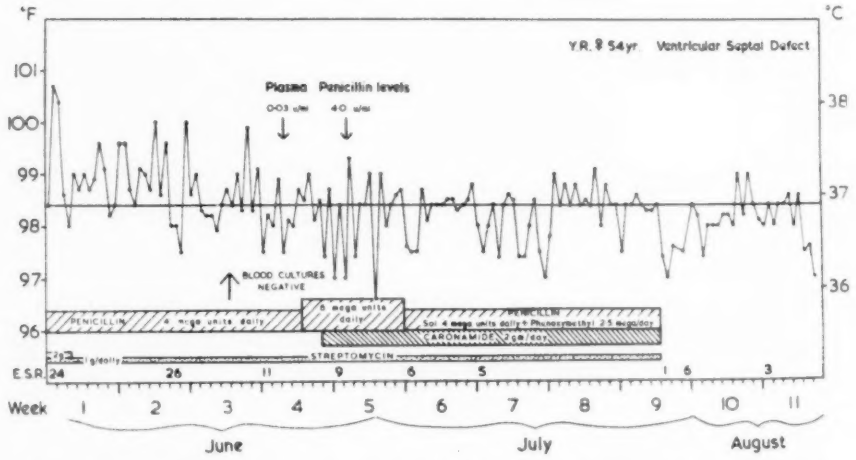

FIG. 3.—Temperature chart and relevant data in a patient with ventricular septal defect in whom the infection was cured without added cardiac damage.

Acute bacterial endocarditis.—The mortality still remains extremely high. Fisher *et al.* (1955) and Shubin *et al.* (1958), reporting on cases of staphylococcal endocarditis, quoted a mortality of from 50–75%, while Morgan and Bland (1959) noted that 85% of 53 patients with acute bacterial endocarditis died. Table II shows the results in a total of 39 cases, 9 acute and 30 subacute. In the acute group only 2 survived. Of the 7 who died, 5 died infected; in the other 2 the infection was cured but death occurred from heart failure, ruptured valve or emboli.

The problem of the patient with negative blood cultures.—It is my impression that patients with negative blood cultures are being seen more frequently. Perhaps this is due to the fact that many patients receive chemotherapy from time to time which tends to mask the infection.

The general experience is that the recovery rate is lower when no positive cultures are obtained than when cultures are positive. This may be due to the fact that the infection is more deep seated and more difficult of access to antibiotic. In the experience of Cates and Christie (1951) and of Friedberg (1950) between 50% and 80% of patients with positive cultures recovered, but only between 20% and 40% of those with negative cultures. Furthermore, congestive heart failure

was three times more frequent when the cultures were negative than when positive (Cates and Christie, 1951). More recently, however, the results in patients with negative cultures have been better. Thus Dormer (1958) reported that 70% of 16 patients recovered, while in the Hammersmith series 9 out of 10 patients with negative cultures were cured, the remaining patient dying of congestive heart failure due to severe congenital aortic stenosis, although the infection had resolved. These better results may be due to earlier diagnosis, and more intensive treatment. The patient should be treated for at least eight weeks with full doses of penicillin and streptomycin, with probenecid in addition. The response of the patient must be assessed from subsidence of fever, increasing hæmoglobin, falling sedimentation rate, and general improvement in well-being. Persistent embolic phenomena indicate that the infection is still active. Blood levels of penicillin may be of great value in assessing treatment, and very high levels can be obtained. In one of the Hammersmith patients, a level of penicillin of 40 units/ml was achieved. The desirable penicillin blood level depends upon the sensitivity of the infecting organism, but where no positive cultures have been obtained this, of course, is not known, and it is therefore wise to aim at a level of at least 10 units/ml as in penicillin-resistant cases (Stuart-Harris *et al.* 1949).

There is a tendency for the fever to recur in patients with negative cultures (Cates and Christie, 1951). Dormer (1958) noted a persistently high sedimentation rate in some patients and suggested that this might be the result of very frequent intramuscular injection of antibiotics over a period of several weeks. In my own experience only 3 of 10 patients with positive cultures had a sedimentation rate of greater than 15 mm in one hour after successful treatment, whereas 6 of 10 patients with negative cultures had such a sedimentation rate under the same circumstances. The tendency for a high sedimentation rate to persist in the negative culture patients presents the clinician with a difficult problem in assessing the possibility of cure. However, if all other signs of infection are absent, the course of treatment has been adequate, and cardiac function is satisfactory, then it is usually safe to assume that the infection has been cured; the sedimentation rate will usually fall gradually over the next four weeks. It is worth noting, however, that an infected tooth socket may be the cause of a persistently high sedimentation rate under these circumstances and meticulous care is necessary in surveying the dental condition. The results in patients with negative cultures may be expected to improve further if the possibility of the condition is constantly borne in mind so that diagnosis can be made early, and adequate treatment with high dosages of penicillin and with streptomycin given for a sufficiently long period.

Relapses.—Patients may suffer from more than one attack of bacterial endocarditis, and the risk of relapse after a six months' cure has been estimated at about 2% per annum. Relapse usually occurs within three weeks of ceasing treatment (Cates and Christie, 1951). The causes of relapse are inadequate treatment, inaccessibility of the lesion to the antibiotic, and a persistent focus of infection. Inaccessibility of the lesion may occur when the infection is deep seated in valve pockets, and is of course an indication that very high blood levels of penicillin are required. Teeth are the most important persistent focus of infection, and wherever necessary total dental clearance should be carried out during (but not after) the course of treatment, preferably in the last two weeks.

Other sources of infection are the prostatic bed and the spleen.

Bacterial endocarditis after cardiac surgery.—The advent of surgery of the heart has posed many problems, one of these being the accidental introduction of infection into the heart during cardiotomy. It is a striking testimony to aseptic technique that this very seldom happens. Denton *et al.* (1957) reported 20 cases of bacterial endocarditis after 2,263 cardiac operations performed between 1950 and 1955. The incidence after operation for congenital heart disease was 1 in 374 patients, and after operation for acquired valvular disease 19 in 1,889. However, when infection occurred it was serious. 14 of the 20 cases were infected with staphylococci, and 12 of these died. At Hammersmith Hospital in a series of nearly 300 mitral valvotomies, there has only been 1 case of mitral valve infection. This was due to *Ps. pyocyanea* and the patient unfortunately succumbed. There has also been one case of infection of the ventricular septum with *Staph. albus* after closure of a ventricular septal defect; the patient made a complete recovery. There have been no other cases in over 100 patients operated upon during total cardiopulmonary bypass.

The dangers of staphylococcal endocarditis following mitral valvotomy, however, have been emphasized by Resnekov (1959) who reported that 14% of 70 consecutive mitral valvotomies were complicated by a staphylococcal endocarditis. 3 patients died.

Conclusions.—It is clear that infective endocarditis is a serious disease, and that early and energetic treatment is essential to prevent pro-

gressive cardiac damage. Prophylaxis is therefore vital. It is probable that an increasing number of patients with negative blood cultures may be seen, and early diagnosis and energetic treatment is of great importance. It is also unfortunately likely that an increasing number of cases of infection with penicillin-resistant staphylococci may occur. It is probable that when the organism is of low virulence infection may be present for many months before the disease becomes obvious, the patient complaining merely of general malaise or increasing cardiac disability. Infective endocarditis should always be considered in patients in whom the cardiac condition deteriorates without obvious cause. This insidious nature of the subacute type of infection is particularly important in elderly people in whom the condition may not be considered.

Finally, whatever the results of blood cultures, in the majority of cases penicillin and streptomycin are the most satisfactory drugs to use. They should not be withheld.

REFERENCES

BERGER, A. R., and KOSSMANN, C. E. (1951) *Ann. intern. Med.*, **35,** 1125.

Brit. med. J. (1960) i, 43.

CATES, J. E., and CHRISTIE, R. V. (1951) *Quart. J. Med.*, **20,** 93.

CHRISTIE, R. V. (1953) *Brit. med. J.*, ii, 438.

CLAWSON, B. J. (1948) *Minn. Med.*, **31,** 1094.

DENTON, C., PAPPAS, E. G., URICCHIO, J. F., GOLDBERG, H., and LIKOFF, W. (1957) *Circulation*, **15,** 525.

DORMER, A. E. (1958) *Brit. med. J.*, i, 63.

—— (1959) *Brit. med. Bull.*, **16,** 61.

DUTTON, A. A. C., and ELMES, P. C. (1959) *Brit. med. J.*, i, 1144.

EAGLE, H., FLEISCHMAN, R., and LEVY, M. (1953) *New Engl. J. Med.*, **248,** 481.

FINLAND, M. (1954) *New Engl. J. Med.*, **250,** 372, 419.

—— (1958) *J. Amer. med. Ass.*, **166,** 364.

FISHER, A. M., WAGNER, H. N., Jr., and ROSS, R. S. (1955) *Arch. intern. Med.*, **95,** 427.

FRIEDBERG, C. K. (1950) *J. Amer. med. Ass.*, **144,** 527.

—— (1956) Diseases of the Heart. 2nd ed. London.

GERACI, J. E. (1955) *Proc. Mayo Clin.*, **30,** 192.

—— (1958) *Med. Clin. N. Amer.*, **42,** 1101.

——, HEILMAN, F. R., NICHOLS, D. R., and WELLMAN, W. E. (1958) *Proc. Mayo Clin.*, **33,** 172.

——, and MARTIN, W. J. (1953) *Circulation*, **8,** 494.

——, —— (1954) *Proc. Mayo Clin.*, **29,** 109.

HAMBURGER, M., and STEIN, L. (1952) *J. Amer. med. Ass.*, **149,** 542.

HOBSON, F. G., and JUEL-JENSEN, B. E. (1956) *Brit. med. J.*, ii, 1501.

JONES, A. M., HERRING, R., LANGLEY, F. A., and OLEESKY, S. (1947) *Brit. Heart J.*, **9,** 38.

LINGEMAN, C. J., SMITH, E. B., BATTERSBY, J. S., and BEHNKE, R. H. (1956) *Arch. intern. Med.*, **97,** 309.

MORGAN, W. L., and BLAND, E. F. (1959) *Circulation*, **19,** 753.

NEWMAN, W., TORRES, J. M., and GUCK, J. K. (1954) *Amer. J. Med.*, **16,** 535.

PRIEST, W. S., SMITH, J. M., and MCGEE, C. J. (1946) *New Engl. J. Med.*, **235,** 699.

——, ——, —— (1947) *Arch. intern. Med.*, **79,** 333.

RESNEKOV, L. (1959) *Lancet*, ii, 597.

SANTOS-BUCH, C. A., KOENIG, M. G., and ROGERS, D. E. (1957) *New Engl. J. Med.*, **257,** 249.

SAPHIR, O., KATZ, L. N., and GORE, I. (1950) *Circulation*, **1,** 1155.

——, and LEROY, E. P. (1948) *Amer. J. Path.*, **24,** 83.

SHUBIN, H., LEVINSON, D. C., and GRIFFITH, G. C. (1958) *J. Amer. med. Ass.*, **167,** 1218.

STUART-HARRIS, C. H., COLQUHOUN, J., and BROWN, J. W. (1949) *Lancet*, i, 99.

TOH, C., and BALL, K. P. (1959) Personal communication.

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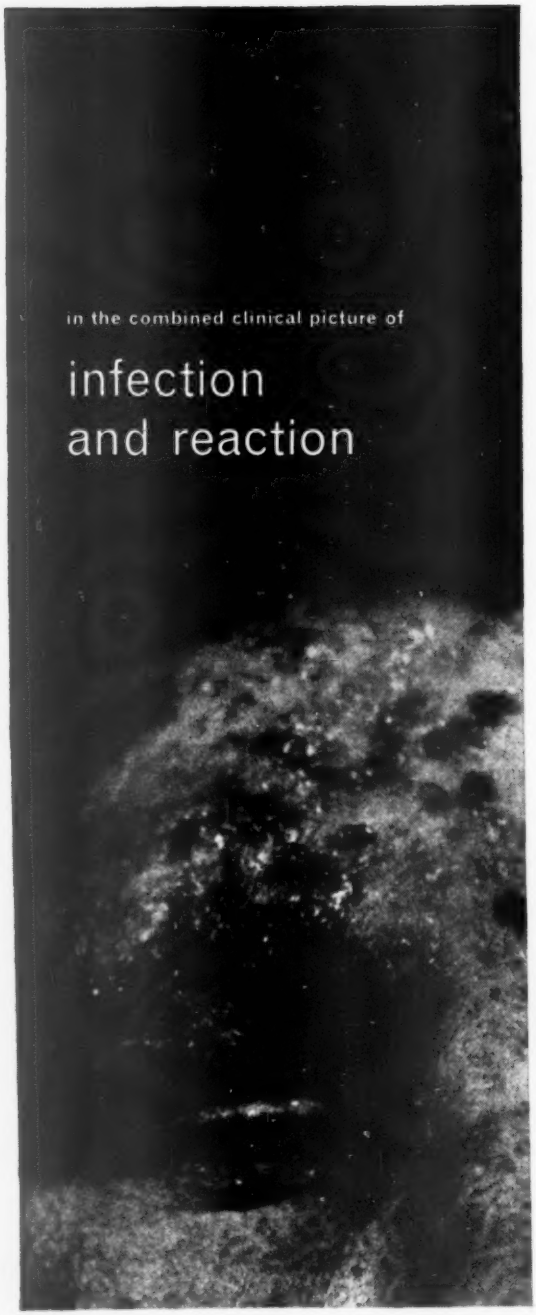

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Section of Dermatology

President—HUGH GORDON, M.C., F.R.C.P.

Meeting
January 21, 1960

Pemphigoid Occurring with Carcinoma of the Rectum.—LOUIS FORMAN, M.D.

Mrs. F. S., aged 70.

History.—August 1958: Irritable erythematous and vesicular eruption on arms and trunk. Treated without success with dapsone, sulphapyridine. Controlled with Ledercort.

February 1959: Bleeding from rectum.

November 1959: Carcinoma of rectum removed by perineal resection. "Adenocarcinoma which had infiltrated the perirectal fat, no lymph glands detected."

A week after the operation severe relapse of the pemphigoid.

Present condition.—Extensive areas of trunk and limbs involved with small and large bullæ.

Investigations.—Hb 76%. W.B.C. 6,800 (polys. 55%, eosinos. 9%, basos. 1%, lymphos. 33%).

Biopsy: Subepidermal œdema and blistering with eosinophils present in large numbers in the infiltrate around the dilated vessels.

Comment.—The relapse probably occurred because the steroid had been inadvertently stopped before the operation, the recovery from which was uneventful. Prednisone has since controlled the pemphigoid. I have seen pemphigoid in a case under Dr. F. Ray Bettley, which occurred following X-ray treatment of carcinoma of the ovaries.

Dr. F. F. Hellier: I can recall several patients who have presented with a pemphigoid eruption in whom there has been some visceral malignant disease, including a carcinoma of the uterus and one of the breast. This association is not uncommon and I believe that every case of pemphigoid should be considered from this point of view and thoroughly investigated to eliminate the possibility of some latent neoplasm.

Dr. H. Wilson: I believe that there is association between pemphigoid and carcinoma. The evidence, however, is largely based on sporadic cases and I feel that a larger series is needed before one can accept the association as proved. I remember treating 2 patients in whom both conditions were present. One of them died from a carcinoma of the stomach, while the other was a woman with an inoperable carcinoma of breast. In her case the pemphigoid eventually cleared up so that the association may or may not have been significant.

Discoid Lupus Erythematosus: Pigmentation of the Nail Beds Following the Administration of Amodiaquine Hydrochloride.—ANNE MAGUIRE, M.R.C.P. (for LOUIS FORMAN, M.D.).

R. G., male, aged 46. Civil Servant.

History.—Discoid lupus erythematosus since 1942, treated with bismuth, five courses each lasting three months. In 1955 he was given chloroquine for five weeks and then amodiaquine hydrochloride, 300 mg daily, which he has received since.

February 1959: His finger nails had become green. On examination all the finger and toe nails were vivid blue-green. No pigmentation elsewhere. His general health, apart from the lupus erythematosus, was good. All investigations at that time were normal. By the end of the year the colour had changed to bluish-grey; it was now known that the pigment was in the nail bed and not in the nail. It was decided to try to ascertain the nature of the pigment.

Two references in the past year on pigmentation occurring with amodiaquine therapy were available. Young (1958) found a brown pigmentation of the skin of the perineal area and grey-yellowish pigmentation of the sclera in 3 patients. He endeavoured to ascertain the nature of the pigment and assumed that two were present: melanin (obtained by ammoniated silver nitrate test) and a derivative of amodiaquine. Campbell (1959) describes pigmentation occurring in a group of patients receiving amodiaquine as a malarial suppressive. The pigmentation was bluish-grey, and occurred on the face, lips, nose and particularly, and most commonly, the nail beds both of fingers and toes. No attempt was made to determine the nature of the pigment.

Investigations.—Two pigmented toe-nail beds were excised. Spectro-fluoroscopy on one was carried out by Professor R. T. Williams (St. Mary's Hospital) with the following results (a normal nail bed was used as control):

	Activation wavelength	Fluorescent wavelength
Pigmented nail beds in solution of normal NaOH	340 mμ	410 mμ
Normal nail beds in solution of normal NaOH	340 mμ	420 mμ
Camoquin in solution of normal NaOH	(*a*) 275 mμ (*b*) 355 mμ	460 mμ

This confirmed that amodiaquine was not present as such in the tissues.

The second pigmented nail bed was sent to Dr. Colin Adams (histopathologist, Guy's Hospital). In order to save the pigment the nail bed was packed in cardice and sectioned fresh on the cryostat. It was revealed that three types of pigment were present:

(1) Hæmosiderin—free iron detected by Perles' ferricyanide test. (2) Lipofuscin—demonstrated by performic acid Schiff and prolonged Ziehl-Neelsen technique. (3) A strong reducing agent—demonstrated by ferric ferricyanide test, and ammoniated silver nitrate methods.

Bismuth (Komaya's method)	Not present
Argentaffin (diazo reaction)	
Chromaffin (adrenochrome reaction)	
Hæmatoidin (Gmelin test)	
Polysaccharide (periodic acid Schiff and alcian blue)	

In the opinion of Dr. Adams the presence in the tissues of free iron and oxidized lipid pigment lipofuscin indicates an old hæmorrhage even though the vessels appeared normal when biopsy was performed.

When extraneous agents are excluded it was thought that a strong reducing agent could only be melanin. However, when amodiaquine was tested *in vitro* with ferric ferricyanide, it gave as strong a reaction as melanin, but chloroquine and quinine did not.

Both chloroquine and amodiaquine are aminoquinolines, but amodiaquine, unlike chloroquine, has a phenolic ring; therefore it was deduced that amodiaquine reduced ferric ferricyanide on account of this phenolic ring.

Other anti-malarials are known to give rise to ochronosis-like pigmentation: Atabrine (mepacrine) used as a malarial suppressive in the Pacific during the war produced similar pigmentation (Cole *et al.*, 1953; Goodman and Gilman, 1955).

In the condition ochronosis, which is associated with alcaptonuria, the pigment which is excreted in the urine and laid down in the tissues is known to be oxidized homogentisic acid. The colour in this condition is bluish black or greyish black.

Homogentisate oxidase is the enzyme which converts homogentisic acid to maleyl-acetoacetic acid in the main metabolic pathway of trytophan, phenylalanine, and tyrosine (La Du *et al.*, 1958).

It may well be that amodiaquine or its complex breakdown products inhibit homogentisate oxidase locally in the tissues causing focal pigmentation.

I wish to thank Dr. Louis Forman, Dr. E. J. Moynahan, Dr. Colin Adams, and Professor R. T. Williams for their help with this case.

REFERENCES

CAMPBELL, C. H. (1959) *Trans. R. Soc. trop. med. Hyg.*, **53**, 215.
COLE, H. N., Jr., CHIVINGTON, P. V., Jr., DRIVER, J. R., and COLE, H. N. (1953) *J. Amer. med. Ass.*, **153**, 1515.
GOODMAN, L. S., and GILMAN, A. (1955) Pharmacological Basis of Therapeutics. 2nd Ed. New York.
LA DU, B. N., ZANNONI, V. G., LASTER, L., and SEEGMILLER, J. E. (1958) *J. biol. Chem.*, **230**, 251.
YOUNG, D. E. (1958) *Ned. Tijdschrift. Geneesk.*, **102**, 1088.

Dr. C. D. Calnan: In Paris two years ago, three or four patients like this were shown at the Rothschild Hospital. They presented large areas of pigmentation over the legs particularly, apart from the nails, and in the mouth. I am most grateful to Dr. Maguire for showing this case and for working it out so beautifully.

Dr. K. V. Sanderson: During the war in the Pacific area I believe a large number of cases of this kind were seen. I saw a number myself, and I know other physicians regarded it as common among troops who were taking at the time mepacrine, 600 mg a week. Another common area for pigmentation was the palate.

Dr. E. J. Moynahan: Is the substance not found in the urine? It must be excreted eventually. One would expect to find quite a lot by feeding these people on amodiaquine. The important thing is, of course, the blueness of the nails. Where pigment is present in a structure like the nail there will tend to be an optical blue coloration and it undoubtedly contributes to the colour, but it is not the whole answer. If there is an enzyme defect I would expect to find something in the urine.

Dr. D. E. Sharvill: Was there any fluorescence of the hair or finger nails?

Dr. A. Maguire: There was no fluorescence of hair or finger nails.

Dr. R. D. Sweet: I have had 2 cases. One got completely well. Neither fluoresced.

Granuloma Inguinale.—P. J. HARE, M.R.C.P.

N. C., male, aged 48. Presser.

History.—Military service in Syria, Palestine, Egypt and Italy before the onset of the lesion about fourteen years ago as a small pimple in the left groin. It steadily enlarged and began to grow more rapidly about two years ago. It has been painless and he was afraid to seek medical advice as he thought that the condition might have been venereal in origin. He received no treatment until after admission to hospital.

Clinical findings.—A mass of firm beefy red vegetations measuring 8 × 6 in. (20 × 15 cm) and

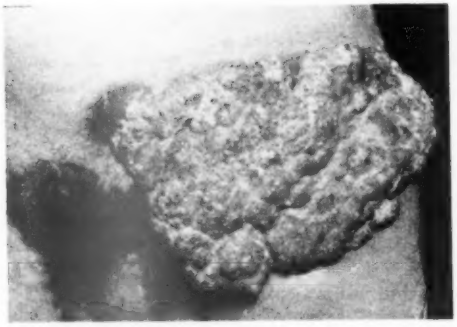

FIG. 1.—Appearance on admission.

projecting 2 in. (5 cm) from the surface of adjacent skin occupies the left groin (Fig. 1). In the crevices between the vegetations there is a copious thin yellowish evil-smelling fluid. No frank ulcer is visible. The vegetations bleed if disturbed. Where the lesion joins the surrounding skin, the latter is purplish brown, firm and shiny. This is best seen at the upper medial border of the lesion. There is no striking adenopathy anywhere, the liver and spleen cannot be felt and he is afebrile.

Investigations.—Blood W.R. and Kahn negative. Frei test negative. Mantoux 1:10,000 negative. Hb 72%. W.B.C. 6,500, polys. 84%. Skiagrams of chest and left knee normal. Biopsy of lesion: pseudo-epitheliomatous hyperplasia of marked degree: dermal infiltrate containing numerous plasma cells, histiocytes and foci of polymorphs. Giemsa stained preparations show a small number of histiocytes containing cytoplasmic granules resembling Donovan bodies.

Comment.—This is regarded as a long-standing case of granuloma inguinale in which pseudo-epitheliomatous hyperplasia has developed from the ulcer.

POSTSCRIPT.—The lesion failed to respond to treatment with streptomycin and chlortetracycline and was excised. Histological examination of the mass gave no new information. There was no evidence of malignant change and the regional lymph glands showed non-specific inflammatory changes. Cultures on chorio-allantoic membrane failed to grow any significant organism.

Group Captain H. E. Bellringer: A number of years ago, when serving in Kurdistan, I saw a case which was almost identical with this, and it turned out to be granuloma inguinale, with the additional feature that the whole dermis had been eroded. When I first saw the patient, a Kurd, he was denuded of skin over the ventral surface of the body from half an inch below the umbilicus to just above the knees. The disease had been present for about ten years. It was so like the present case that one supports the diagnosis on clinical grounds.

Dr. C. D. Calnan: I should like to support Dr. Hare's diagnosis, although these cases are difficult. I saw a case of granuloma inguinale in a negro in America recently, where it is not uncommon. The patient had had three or four biopsies over a few years, and, because neoplastic change was not confirmed, no surgery was carried out. Eventually there was confirmation of carcinoma but by that time it was too late; the lymphatics go deep into the pelvis. I should have thought that the risks supported early surgery.

Dr. Louis Forman: I have under treatment a man with a giant warty mass filling the internatal cleft and spreading the buttocks apart. The epithelium showed a gross simple hypertrophy and marked papillomatosus. The diagnosis was a non-malignant virus wart. The appearance of the warty epithelium in Dr. Hare's patient is very similar to that seen in my case.

Dr. C. D. Calnan: I am merely suggesting that we should not wait too long. The patient is having chemotherapy at the moment.

The following cases were also shown:

Two Cases of Cutaneous Vasculitis.—Dr. LOUIS FORMAN.

Atopic Eczema, Ulcerative Colitis, Hepatosplenomegaly.—Dr. A. W. MCKENZIE (for Dr. LOUIS FORMAN).

(1) Leukoplakia of the Tongue and Cheeks. ? Due to Arsenic. ? Due to Peppermint. (2) Multiple Basal Cell Metaplasia and Bowen's Disease. Arsenical Keratomata of Palms and Soles. (3) Urticaria Pigmentosa with Hepatosplenomegaly.—Dr. LOUIS FORMAN.

Rhizopus Parasitica: Infection of Forearms.—Dr. E. J. MOYNAHAN.

Urticaria Pigmentosa.—Dr. W. C. MARSHALL (for Dr. E. J. MOYNAHAN).

Hyperkeratosis of Palms and Soles and "Periodontosis" (Papillon-Lefevre Syndrome).—Dr. E. J. MOYNAHAN and Mr. W. G. CROSS.

Brevicollis (Klippel-Feil Syndrome). Diastematomyelia. Satyr's Tail.—Dr. V. R. BLOOM (for Dr. E. J. MOYNAHAN).

Case for Diagnosis. ? Hamartoma.—Dr. E. COLIN-JONES.

Pseudoxanthoma Elasticum.—Dr. D. SHARVILL.

Cicatricial Alopecia: Lupoid Sycosis.—Dr. PETER SMITH.

Dermatitis Traumatica of the Lips, Cured by Hypnosis.—Dr. M. J. FENTON.

Meeting
February 18, 1960

Bisalbuminæmia with Curious Acrocyanotic Skin Changes (Two Cases).—D. I. WILLIAMS, F.R.C.P.

Case I.—B. B., male, aged 16½. Schoolboy.

History.—This boy's hands have always been intensely cold, blue and rather clammy. He noticed three years ago that the little fingers were gradually becoming bent, and more recently the ring, middle and index fingers have begun a similar change but to a lesser degree. His fingers never become white with cold. His feet have been normal.

Family history.—He is an only child. His father shows similar changes without the contracture of the fingers but with the addition of cold, blue feet (Case II). His grandfather now dead, apparently had similar hands.

Clinical findings.—On examination the hands are remarkably blue, cold and usually clammy. The fingers of each hand cannot be straightened: it is very difficult to explain this. It seems almost as if the skin no longer fits his fingers. There is hyperkeratosis rather like knuckle pads over the proximal interphalangeal joints. There is a cobblestone hyperkeratosis, most marked around the nail folds, which appears to be an exaggeration of normal skin markings. There are two or three permanent white areas amongst the blue.

Investigations.—Hb, W.B.C., E.S.R., transaminases, urine, serum electrolytes, blood urea, serum calcium, plasma phosphorus, serum proteins, liver function tests, ECG, all normal. No cryoglobulins detected. Cold agglutinins detected to a titre of 1:16. X-rays of chest, cervical spine, hands, barium swallow and follow through normal. Biopsy of skin: section shows some hyperplasia of the epidermis which has an irregular "saw-tooth" external surface and is producing abundant dense keratin. The dermis is normal. There are no specific features.

Case II.—R. B., male, aged 52. Foreman.

History.—Cold hands and feet all his life.

Family history.—His father and son have similar hands.

Clinical findings.—On examination his hands and feet are cold, usually clammy, and blue. There is a fine mosaic type of hyperkeratosis mainly around the nail folds and one permanent white area on the left big toe.

Investigations.—The only interesting finding has been that of bisalbuminæmia.

Comment.—When I first saw the son, and later the father, I had no doubt that the condition of the skin of the hands and the pattern of partial immobility of the fingers and wrists were not acrosclerosis nor a simple acrocyanosis. The surprising finding of bisalbuminæmia in these two patients and in several of their relatives naturally led to speculation of the possible relationship between the skin and albumin changes. Professor N. H. Martin will describe his findings and the family tree. It could be argued that these two extremely rare and curious conditions running through this family are unrelated: on the other hand, it is tempting to think that the presence of an abnormal albumin in the skin and in the tissues around the joints may be playing at least some part in the obvious clinical changes. Some members of the family have the abnormal albumin without the skin changes: so that something more than this abnormality alone would be required for the abnormalities of the skin to be clinically evident.

Professor N. H. Martin: The family tree is shown in Fig. 1. The open small circles represent members of the family we cannot trace, the open large circles members examined and shown to be normal. The boy and his father are shown thus ● as are all other members of the family who displayed the albumin abnormality. An uncle and an aunt, as well as her son and granddaughter, all displayed this unusual serum protein abnormality.

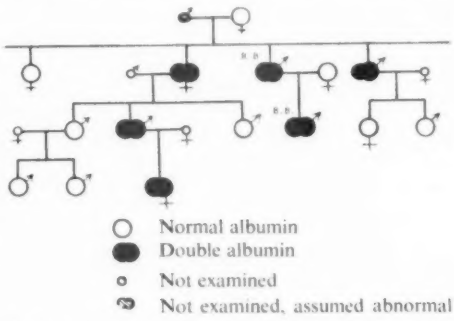

FIG. 1.—Family tree of the affected family. R.B. and B.B. both suffered from skin lesions.

Fig. 2 shows electrophoretic analysis on paper of the father and son flanked by normal controls. The unusual splitting of the albumin is seen clearly. These analyses were confirmed by classical electrophoresis and the two albumins separated for further examination on a starch block. They were examined by immunological techniques and behaved in an identical manner to a series of specific antisera. Moreover, their behaviour in binding a series of specific dyes was identical. We have done amino-acid microanalysis and, up to the present time, the only

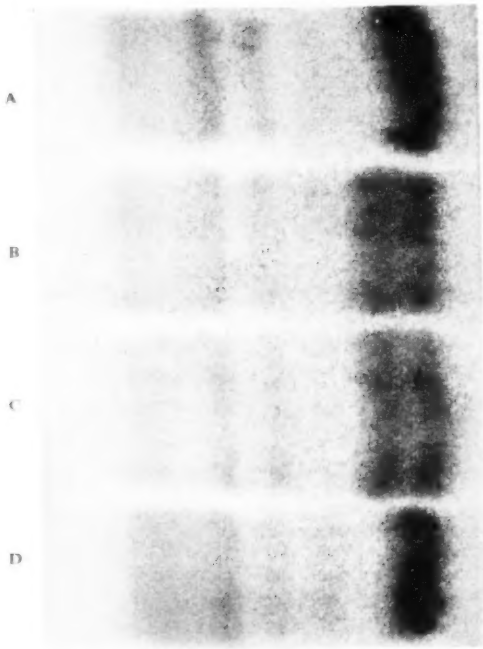

FIG. 2.—Electrophoretic analysis carried out on paper in pH 8·6, 0·05 Molar barbiturate buffer, with a current of 0·2 mA/cm cross section. A and D, normal controls. B, analysis of the father's serum. C, analysis of the son's serum.

abnormality we can find is the difference in the electrical mobility which does not amount to more than one or two units of charge.

In 1956 Dr. M. E. Mackay and I made a careful study of the reaction of human albumin to heat. We found that under carefully controlled conditions at 56° C, albumin would split into two components demonstrable by electrophoresis. This did not appear to be associated with fragmentation of the molecule and we wondered whether it could not be the result of unfolding of the albumin with molecular reorientation.

The beautiful work of Perutz and his colleagues (1960) on the intricate folding of hæmoglobin is well known. We wondered whether the difference between the two albumins in this family might not depend on alteration in the folding of albumin—as if nature in this instance had tied a "reef-knot" in 50% of the molecules and a "slip-knot" in the remainder. Sailors will appreciate the potential dangers of such an error. Humphrey *et al.* (1957) have shown that there is a considerable amount of albumin in the skin. It is tempting to think, therefore, that if the albumins with the "slip-knot" in them failed to do their jobs, might not the skin be the place in which one would see manifestations of their failure. However, the four other members of the family, whose serum also contains abnormal albumin, have no skin lesions. Of course we do not know whether the "reef" or the "slip" knot is the normal configuration.

If this abnormality is gene-linked, it is a dominant heterozygotic character. It is natural therefore to compare it with gene-linked abnormalities such as the sickle cell trait. However it does differ in one striking way from the sickle cell families. Whereas the amount of abnormal hæmoglobin in the sickle cell trait can vary between 20% and 50%, in all the persons examined with bisalbuminæmia the two albumins were present in about equal proportions.

REFERENCES

HUMPHREY, J. H., NEUBERGER, A., and PERKINS, D. J. (1957) *Biochem. J.*, **66**, 390.
MACKAY, M. E., and MARTIN, N. H. (1956) *Biochem. J.*, **65**, 284.
PERUTZ, M. F., ROSSMANN, M. G., CULLIS, A. F., MUIRHEAD, H., WILL, G., and NORTH, A. C. T. (1960) *Nature, Lond.*, **185**, 416.

Darier's Disease Presenting with Dystrophy of the Nails.—K. M. HARVEY, M.B. (for P. J. HARE, M.R.C.P.).

J. C., female, aged 13. Schoolgirl.

History.—Two years ago this girl presented with a three-year history of distortion and lack of growth of the finger nails complicated by recurrent painful paronychia. The toe nails were not affected. There was a history of nail biting and enuresis but Dr. Hare regarded the condition as being congenital in origin even though of late appearance.

Six months ago she developed discrete, brownish warty lesions on the side of the neck and the dorsum of the hands. The latter have cleared coincident with or influenced by oral vitamin A (150,000 i.u. daily).

At the age of 5 she was investigated for abdominal pain and recurrent intestinal hæmorrhage and the possible diagnosis of von Willebrand's disease (pseudohæmophilia) was made. All hæmatological investigations including capillary microscopy were negative and since that time there has been no recurrence of symptoms.

Family history.—Younger sister has von Willebrand's disease but her skin and nails are normal.

Examination.—The finger nails of both hands are dystrophic and some show mild paronychia. There are discrete brownish warty lesions on both sides of the neck. Repeated examination of nails for fungus gave negative results.

Histology.—Darier's disease showing typical intra-epidermal clefts containing acantholytic cells.

Comment.—Spitzer (1921) in his review of the literature of nail changes in Darier's disease quoted a family in which the skin changes of Darier's disease and nail changes had been known to be present in three successive generations. In the third generation nail changes were present at birth and the typical skin lesions did not develop until the age of 14 years.

REFERENCE

SPITZER, R. (1921) *Arch. Derm. Syph., Berl.*, **135**, 370.

The following cases were also shown:

Calcinosis Circumscripta Helicum.—Dr. D. I. WILLIAMS.

Meeting
March 17, 1960

Cutaneous Arteriolitis.—R. H. CHAMPION, M.B., M.R.C.P., and ARTHUR ROOK, M.D.

L. B., aged 75. Retired.

History.—For three years this man has had recurrent crops of lesions on the limbs and body associated with intense irritation.

Most of his lesions, especially those on the body, presented as excoriations suggesting a prurigo. However, close observation in hospital has shown a variety of lesions at different times including some resembling erythema multiforme, purpuric macules, hæmorrhagic nodules and ulcers. Others seem to be simple excoriations.

Past history.—Gastro-enterostomy for chronic peptic ulcer in 1959.

On examination.—Scattered almost uniformly over the body and limbs are many pigmented scars, 5–10 mm across, and large excoriations. On the legs are a few purpuric macules and hæmorrhagic nodules, some of which have progressed to form ulcers up to 5 cm across.

No abnormality on general examination. Blood pressure 130/80.

Investigations.—Blood count normal, no eosinophilia. E.S.R. 10 mm in first hour (Wintrobe). Plasma proteins normal. W.R. negative. Urine normal. Chest X-ray normal.

Biopsy of a recent nodule: Many of the blood vessels in the dermis show fibrinoid necrosis; their walls and the surrounding connective tissue are heavily infiltrated with neutrophil polymorphs, many of which are degenerate, and with macrophages.

Comment.—This patient has an unusually extensive cutaneous arteriolitis without any evidence of systemic disturbance. He seems to fit into the group described by Ruiter as arteriolitis cutis allergica and by the French as allergides nodulaires of Gougerot. Such intensive irritation would seem to be unusual and we have wondered whether to consider this a senile prurigo unrelated to the vasculitis.

Case for Diagnosis.—Dr. R. H. MARTEN.

Anetoderma (Schweninger and Buzzi).—Dr. I. SARKANY (for Dr. D. I. WILLIAMS).

Polyarteritis Nodosa.—Dr. P. HALL-SMITH.

Temporal Arteritis—Ischæmic Ulcers of Scalp.—Dr. J. EVERALL (for Dr. G. B. MITCHELL-HEGGS).

Lichen Sclerosis of the Penis.—Dr. J. EVERALL.

Oil Melanosis.—Dr. C. HODGSON (for Dr. M. FETWELL).

Dr. W. FRAIN-BELL read a paper entitled **Grenz Rays in the Treatment of Benign Dermatoses.**

Dr. C. H. Whittle: In the absence of a prior claim I would have described this as a case of Church's disease (Church and Whittle, 1950). There were itching lesions 1 cm in diameter, at times hæmorrhagic, similar to, and distributed in much the same way as the present patient's, but more on the upper trunk. The condition recurred in bouts and with each relapse there was some fever. The biopsy showed a wedge-shaped area of necrosis. There were certain differences between Church's cases and this one: Church's patient had a persistent eosinophilia, and the patient was younger, 33 years of age.

The relationship already mentioned with duodenal ulceration is important. Our patient was put on steroids, about which at that time we knew less than we do to-day; but he died, and at autopsy was found to have had no less than four perforations of the gut.

REFERENCE CHURCH, R. E., and WHITTLE, C. H. (1950) *Brit. J. Derm.*, **62**, 408.

Dr. Louis Forman: I am not certain that steroids are indicated in cases of cutaneous arteriolitis which are not associated with evidence of allergy, e.g. eosinophilia and fever. If similar vascular lesions occur in the bowel, perforation might be facilitated if the patient were under treatment with steroids.

If one compares the vascular lesions of cutaneous arteriolitis (or, as I prefer to call the disease, vasculitis, because I am not sure which part of the vascular arcade is affected) with the Schwartzman reaction in rabbits, the observation by Rostenberg (1953) may be important. He quotes from Thomas and Good (1952) that adequate treatment of the rabbit with cortisone seems to serve as a substitute for the preparatory intravenous injection of micro-organisms or their products necessary to sensitize the vessels to a subsequent injection of the same or other organisms.

Recently a patient, with severe scleroderma and known to be mildly hypertensive, while on prednisolone 20 mg daily developed a severe hypertension, extensive retinal hæmorrhage and fatal uræmia, suggesting a rapid deterioration of the renal blood vessels due to the effect of the steroid.

REFERENCES ROSTENBERG, A. (1953) *Brit. J. Derm.*, **65**, 389. THOMAS, L., and GOOD, R. A. (1952) *J. exp. Med.*, **99**, 605.

(Meeting to be continued.)

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*REFERENCES

Welsh, A. L., and Ede, M.: J.A.M.A. 166 : 158, 1958

Additional Clinical Publications on Tarcortin:
Clyman, S. G.: Postgrad. Med. 21: 309, 1957

Bleiberg, J.: J.M. Soc. New Jersey 53 : 37, 1956

Abrams, B. P., and Shaw, C.: Clin. Med. 3 : 389, 1956

Bleiberg, J.: Am. Practitioner 8 : 1404, 1957

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References: "Clinical Medicine," Vol. 5, No. 4, April, 1958; and "Ohio State Medical Journal," Vol. 55, No. 6, June, 1959.

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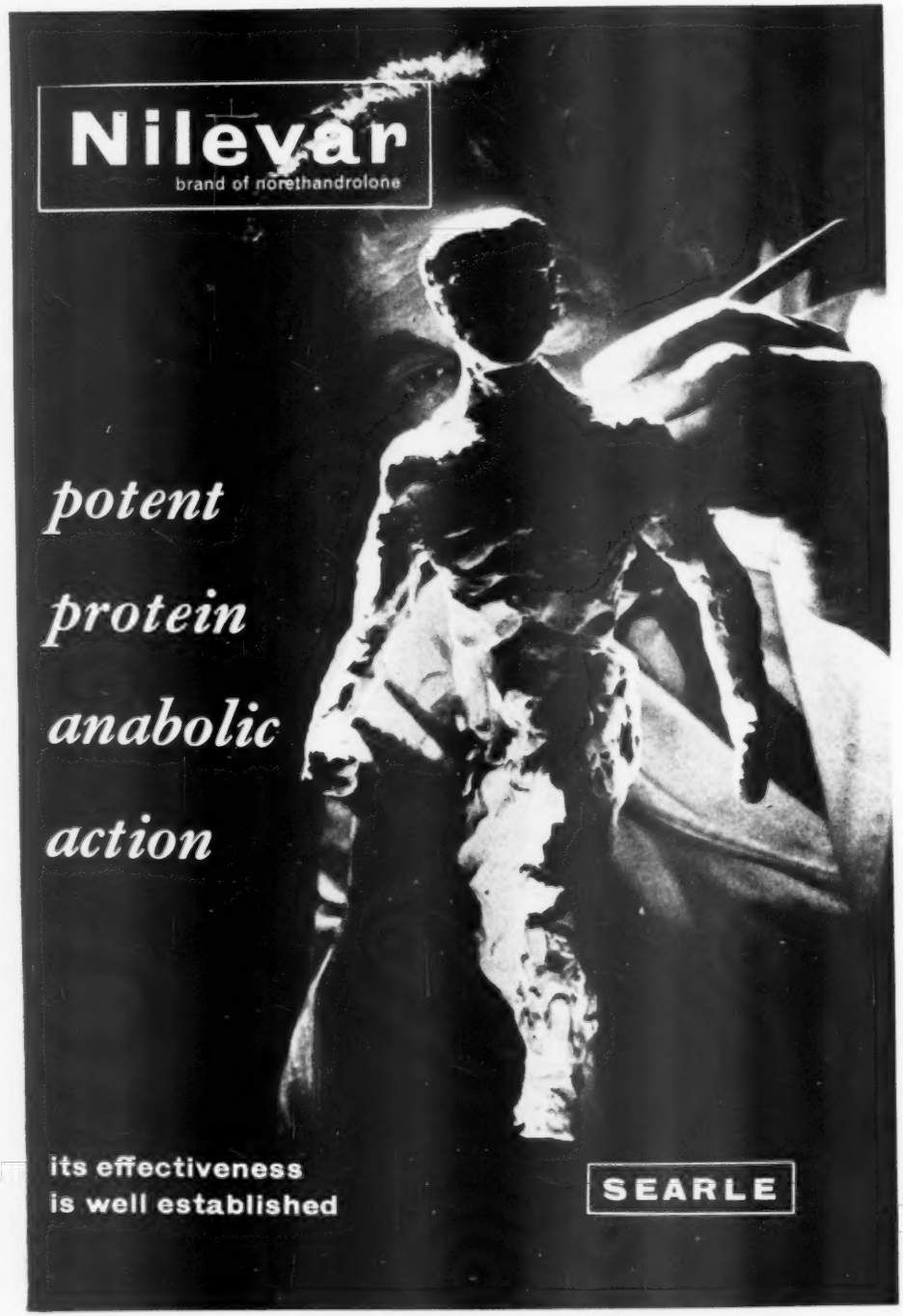
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Section of the History of Medicine

President—CUTHBERT E. DUKES, O.B.E., M.D.

Meeting
March 2, 1960

George Henry Lewes and His "Physiology of Common Life", 1859

By R. E. SMITH, F.R.C.P.
Rugby

IT is right that this Section should commemorate the centenary of the first book in English on Physiology. Volume I appeared in 1859, the second volume in 1860; it was serialized in the *Cornhill Magazine*. Its author, George Henry Lewes lived for many years with George Eliot, that remarkable woman whose novels enjoyed a fame and authority because (to quote Trevelyan, 1945) "They were taken by many as restating the moral law and process of soul-making, in terms acceptable to the rationalist agnostic conscience". She kept a journal and records (Cross, 1885*a*) in a letter to Lewes' son in July 30, 1859:

"The first volume of the 'Physiology of Common Life' is just published, and it is a great pleasure to see so much of your father's hard work successfully finished. He has been giving a great deal of labour to the numbers on the physiology of the nervous system, which are to appear in the course of two or three months, and he has enjoyed the labour in spite of the drawback of imperfect health, which obliges him very often to leave the desk with a hot and aching head. It is quite my worst trouble that he has so much of this discomfort to bear; and we must all try and make everything else as pleasant to him as we can, to make up for it."

George Henry Lewes, who was born in 1817 and died in 1878, was a "comprehensive man". He was at school in England and France, and much of his youth was spent in Germany. He started to walk the hospitals but a dislike of seeing people in physical pain made him abandon medicine. In 1840 he married Agnes, daughter of Swynfen Stevens Jervis, M.P. for Bridport. He became part critic, part composer, two of his plays being "The Noble Heart" and "The Ghost of Speculation". He also wrote novels and his "Ranthorpe" and "Rose, Blanche and Violet" are considered sufficient evidence that he had little influence on the literary style of George Eliot. In 1850 Thornton, Leigh Hunt and he established *The Leader* and he met Miss Evans when she came to London to help to edit the *Westminster Review*. Here the romance with Mary Ann Evans (or, as she preferred, Marion Evans) began and the situation became so complicated that he took her to Germany, there passing as her husband. He finished his life of "Goethe" and returned to England in 1855. Two years later, Miss Evans became a popular authoress on the publication of her "Scenes from Clerical Life". Meanwhile Lewes was pursuing biological studies including marine zoology at Ilfracombe. In 1865 he became the editor of the *Fortnightly Review* and meanwhile he had published his "Physiology of Common Life". In 1874 the 1st volume of "Problems of Life and Mind" appeared, followed the next year by the 2nd and in 1877 by the 3rd, the 4th and last volume being published posthumously. He was short and slight with a fine brow and bright eyes but otherwise, as Douglas Jerrold stated, he was "the ugliest man in London" (Figs. 1 and 2) and he apparently was in poor health for twenty years before his death. In his last illness he was attended by Sir James Paget and Mr. Quain who, a few days before his death, had pronounced him in all respects better.

"Physiology of Common Life" though it presents the knowledge of a hundred years ago, is a provocative book. Electrolyte control is foreshadowed by

"Indeed, so great are the services of salt, that we may confidently accept the statement of Dr. Bence Jones, that it is 'a substance as essential to life as nitrogenous food, or non-nitrogenous food and water'."

These were the days when Liebig had laid emphasis on albumin, and food was divided into Nitrogenous and Non-Nitrogenous. Lewes maintained "Not a cell, not a fibre can be formed, nor can subsist, without a certain amount of fat and salts", a rebuttal of Liebig's theory that nitrogenous food is the only one which is "plastic", i.e. could produce tissues. He objected to one element being selected as indispensable. The brain contains more fat than albumin, neither of which is plastic by itself without water. To emphasize the fallacy of relying on chemistry as a guide to the plasticity of food he quoted Pereira: "Dogs fed for 120 days solely on raw meat, from sheep's heads, preserved their health and weight during this period, the daily consumption never exceeding 300 grammes, and often less. But 1,000 grammes of isolated fibrin, with

National Portrait Gallery.

FIG. 1.—George Henry Lewes. From a water-colour sketch by Anne Gliddon, November 1840.

the addition of some hundred grammes of gelatine and albumin, were insufficient to support life. What, then, is this peculiar principle which renders meat so perfect an aliment? Is it odorous and sapid matter which has this function, as seems probable? Do the salts, the trace of iron, the fatty matters and the lactic acid, contribute to the nutritive effect, notwithstanding that they constitute so minute a portion of meat?"

George Eliot records the meeting of Lewes and Liebig at Munich in 1858 (Cross, 1885*b*):

"There is no one we are more charmed with than Liebig. Mr. Lewes had no letter to him—we merely met him at an evening party; yet he has been particularly kind to us, and seems to have taken a benevolent liking to me. We dined with him and his family yesterday, and saw how men of European celebrity may put up with greasy cooking in private life. He lives in very good German style, however; has a handsome suite of apartments, and makes a greater figure than most of the professors. His manners are charming—easy, graceful, benignant, and all the more conspicuous because he is so quiet and low-spoken among the loud talkers here. He looks best in his laboratory, with his velvet cap on, holding little phials in his hand, and talking of Kreatine and Kreatinine in the same easy way that well-bred ladies talk scandal. He is one of the professors who has been called here by the present king—Max—who seems to be a really sensible man among kings; gets up at five o'clock in the morning to study, and every Saturday evening has a gathering of the first men in science and literature, that he may benefit by their opinions on important subjects."

In defending the proverb, "One man's meat is another man's poison" Lewes foretells the advent of allergy.

"There are persons, even in Europe, to whom a mutton-chop would be poisonous. The celebrated case of the Abbé de Villedieu is a rare, but not unparalleled example of animal food being poisonous: from his earliest years his repugnance to it was so decided, that neither the entreaties of his parents nor the menaces of his tutors could induce him to overcome it. After reaching the age of thirty on a regimen of vegetable food, he was over-persuaded and tried the effect of meat soups, which led to his eating both mutton and beef; but the change was fatal: plethora and sleepiness supervened, and he died of cerebral inflammation."

British Museum.

FIG. 2.—George Henry Lewes. From a drawing by Rudolph Lehman, June 1867.

In reading this book it is necessary to remember it was first serialized in the *Cornhill Magazine* and the readers were mostly lay. He illustrates physiological principles by historical events. Thirst as a torture is vividly expressed by the suffering of those in the Black Hole of Calcutta, and the necessity of fresh air by the disaster in the "Londonderry" plying between Liverpool and Sligo; because of a rough sea the captain and mate incarcerated 200 steerage emigrants in a cabin 18 feet long, 11 feet wide and 7 feet high, resulting in the death of 72. He answers the question "Is sugar injurious to the teeth" by saying, "We have only to point to the Negroes, who eat more sugar than any other human beings, and whose teeth are of enviable splendour and strength". His phrases flow freely, "Timid parents may therefore check their alarm at the sight of juvenile forays on the sugar-basin when not excessive; may cease to vex children by forbidding moderate commercial transactions with the lollypop merchant, and cease to frustrate their desires for barley-sugar by the never-appreciated pretext, that the interdict is 'for their good'." He attacks teetotalism in a temperate manner and deplores the injurious effect of tight lacing: "In England, at least, women have pretty generally learned to see the danger, if not always the hideousness, of those wasp-waists once so highly prized." Vinegar in his day was a cure for obesity. His example is of a woman who drank a glass of vinegar daily and lost her plumpness—but a dry cough developed into a moist one, fever, difficulty in breathing, wasting, night sweats followed and diarrhœa ended her life. "Therefore, young ladies, be boldly fat! never pine for graceful slimness and romantic pallor; but if Nature means you to be ruddy and rotund, accept it with a laughing grace." He records the experiments which convinced many Frenchmen that the horse was edible, and at that time an immense mass of excellent animal food was within their reach which was being wasted because of prejudice.

Blood transfusions though very ancient were being scientifically explored three hundred years ago. He quotes Denis of Paris, who, in 1667, gave a madman who arrived naked in Paris,

eight ounces of calf's blood intravenously. He slept well and next day the operation was repeated and after another good night's sleep, awoke sane! "The tidings flew over Europe" but deaths quickly followed. Even by 1818 success appears to be judged by the resurrection of moribund cases. One interesting observation he makes is that "The blood is always young, for it is always being renewed—Between the blood of an infant and the blood of a patriarch, no appreciable difference can be found".

He gives a good account of digestion and how the aliments are absorbed into the blood, which he describes as, "A mighty river of life". His chapters on "Respiration and Suffocation" and "Why we are warm and how we keep so" are illustrated by negatives such as, "Varnished eggs will not develop", "Carbonic acid not a poison", "Trees not beneficial to streets" and the notion that "Hardening infants is erroneous".

There have always been great names in this country in physiology. Lewes gives credit to Lower and Blundell for their work on transfusion; to John Hunter for his work on hibernating mammals; to Sir Charles Bell, whose claim to fame is not his palsy but his "unimpeachable" discovery that the anterior root carries motor and the posterior root carries sensory fibres. He states Harvey discovered the fact of the circulation despite his ignorance of capillaries and lymphatics. The valves in the veins, "opening and closing like doors," were first noted in 1574 by Fabrice d'Acquapendente under whom Harvey studied at Padua. This knowledge brought the discovery of the circulation within compass. "Harvey not only conceived a clear idea of this process, he described it minutely and accurately." Capillaries were described four years after his death. The lymphatics were discovered a decade before. At the end of an exhaustive chapter he states

"As an episode in the History of Science, the discovery of the circulation will always command the interest of readers; and if the foregoing sketch has had the good fortune to secure the attention of any medical readers, we hope it may have the further effect of inducing them to go carefully through the immortal works of William Harvey."

Our debt to Lewes for increasing our knowledge of the central nervous system is threefold. Firstly his own contributions; secondly his review of facts and theories a hundred years ago and, thirdly, the studentship founded in his memory, of which I shall speak later, and held for four years by the greatest of all neurophysiologists, Sir Charles Sherrington. The second volume of the "Physiology of Common Life" contains five long chapters on "Various Aspects of the Nervous System" and one each on "Sleep and Dreams", "The Qualities we inherit from our Parents", and "Life and Death".

The author himself had made more than a thousand preparations and he had only seen in half a dozen a direct connexion between nerve cells and fibres, "therefore, to make this supposed connexion between cells and fibres the basis of any physiological inferences, will be in the highest degree incautious".

His theory was that cells were grouped together often in ganglions. Though he accepted as unimpeachable Sir Charles Bell's observations on motor and sensory nerves, he built up an elaborate theory that sensibility was the property of ganglionic tissue, and neurility the property of nerve fibres. "When a nerve fibre is stimulated, its neurility is called into play. If the fibre be in connexion with the brain, or spinal cord, the effect is a sensation. If the fibre be in connexion with a muscle, the effect is contraction. If the fibre be in connexion with a gland, the effect is secretion." Lewes presented his views with energy at a meeting of the British Association in Aberdeen. He certainly used vivisection on frogs but it was painless and the knowledge gained, he stated, will lessen human suffering.

"All my friends know my great fondness for animals of every kind, and the almost excessive shrinking from the sight of pain which renders it unendurable for me to see animals suffering. Had it not been for the discovery of ether and chloroform, I should never have pushed my investigations to the length of experiment of live animals, where great pain could be supposed to follow. But it is now becoming almost universal, not simply out of tenderness to animals, but out of regard for accuracy, to render animals insensible before performing any serious operation."

Some of his experiments were simple human ones. His phrase "Reflex-feeling" was the forerunner of conditioned reflexes. The best example he gives is :

"I remember once trying the experiment on a wearied waiter, who had fallen asleep in one of the unoccupied boxes of a tavern. His arm rested on the table, and his head rested on his arm; he snored the snore of the weary, in spite of the noisy laughter and talk of the guests. I called out 'Johnson', in a loud tone. It never moved him. I then called out 'Wilson', but he snored on. No sooner did I call 'waiter', than he raised his head with a sleepy 'yessir'. Now, to suppose, in this case, that he had *no* sensation when the word 'waiter' reached his ears, is to suppose that two similar causes will not produce a similar effect. The dissyllable 'Johnson' would excite as potent a reaction of his Sensibility as the dissyllable 'waiter': but the secondary sensations —the reflex feelings—were different, because the word 'Johnson' was not associated in his mind with any definite actions, whereas the word 'waiter' was so associated as to become an automatic impulse."

In the preface to Vol. II he says:

"It is in the chapters on the Nervous System that the greatest amount of dissent from current opinions will be found; and it is there that the reader will most probably feel the greatest difficulty in agreeing with me, especially if he be versed in the doctrines of the schools, and not very familiar with the subjects through direct observation and experiment. I can only say that the views there put forth are the result of very considerable research, embracing molluscs, bees, beetles, spiders, locusts, crabs, fishes, frogs, tritons, lizards, chickens, moles, mice, rats, cats, dogs, sheep, pigs, calves, oxen and men."

Perhaps this was because he was in advance of his time. The nervous system certainly excited his interest. The kidney is barely mentioned. Interest in the Ductless Glands initiated by Addison was too recent for inclusion.

It would be kinder to remember Lewes as the benefactor rather than as the experimenter. Greater than he in his generation was Claude Bernard who explained sensibility in muscles and contractibility in the skin by boldly assuming "that the posterior nerves sent off filaments to the muscles, and the anterior nerves sent off filaments to the skin". It would be most ungenerous if we judged the greatness of this generation by the few errors they made.

He concluded, "No Scientific subject can be so important to Man as that of his own life. . . . Science passes from its laboratories into the public thoroughfares". The work was serialized and he "received such cheering and generous encouragement from the profession and the public, during the course of monthly publications, as fully to repay the great pains and labour bestowed on the work".

An account of this book would be incomplete without mentioning the sources of information. French authors are freely quoted, especially Claude Bernard then in his heyday. In the many German references, Liebig's "Chemical Letters" is the most frequent source of information. In his preface he apologizes for his deficiency in not quoting English authorities because "My purse is not long enough to command the Transactions, Journals, and Reviews in which my countrymen have recorded their labours; and I have not the advantage of commanding a public library".

George Henry Lewes died on November 28, 1878. In George Eliot's journal on January 2, 1879, she notes "A kind letter from Professor Michael Foster of Cambridge, offering to help me on any physiological point". On January 19, 1879, Clifford Allbutt, an old friend and probably the physician whom she portrayed as Dr. Lydgate in "Middlemarch", wrote to her from Leeds (Haight, 1954–5). He addressed her, "My dear Mrs. Lewes", and opened thus, "It is not too late I trust for me to add my single voice to the many who have sought to console you in your great bereavement." The letter is fulsome and he records that more than one of our best young biologists told him, "Other books on physiology may be more learned and at any rate more comprehensive but although I knew all school physiology as a lesson this knowledge never sprang into life within me until I read Lewes. From him I date my real beginnings". There is a footnote that I. P. Pavlov (1849–1939) said the same. In her reply to this letter which was "Among the most precious signs of sympathy that my kind friends have given me" she asked for any suggestions as to "Founding some lectureship or other efficient instrument of teaching biology (including psychology) in memory of my husband and to be called by his name".

On March 9, 1879, George Eliot records in her journal that "Mr. Henry Sidgwick came to discuss the plan of studentship". And on March 13 that "Professor Michael Foster came to discuss the studentship and we arrived at a satisfactory clearness as to the conditions. He mentioned as men whom he had thought of as suitable trustees, Huxley, Pye Smith, Thiselton Dyer, Francis Balfour, and Henry Sidgwick". On July 2, 1879, she records in a letter to Madame Bodichon (Cross, 1885*c*): "I enclose a copy of Michael Foster's draught of conditions for the studentship, which I put into the lawyer's hands some ten or twelve days ago, and which has now come to me drawn up in legal form." This was at a time when she herself was ill and was "partly fed on 'poisonous decoctions'". Sir James Paget and Dr. Andrew Clark supervised her "excellent country doctor Mr. Parsons".

Cambridge has been a breeding ground for physiologists. Many in the course of their careers have been nurtured by two studentships, the Michael Foster and the George Henry Lewes. Sir Humphry Rolleston (1932) says the Studentship was founded "To advance the study of physiology by supplying students of either sex with the means of pursuing original investigations during the interval between their novitiate and their attaining the status of Professor". The capital sum of £5,000 provided an annual income of £250 for the student who might hold it for one, two, three or in exceptional instances more years, but must devote his or her whole time to the work. The trustees appoint as director a physiologist of established reputation who is in charge of a physiological laboratory in Great Britain. So far the director has always been the Professor of Physiology at Cambridge.

The first student was Charles Roy, strongly

recommended by Michael Foster and "nominated" by George Eliot. It is natural that from the beginning the studentship was open to women. Possibly the influence of "Dearest Barbara", as George Eliot addresses Madame Eugene Bodichon, played a significant part in determining this and choosing Cambridge as the first place at which the student should work. Madame Bodichon (1827–1891) was the daughter of Mr. Leigh-Smith, M.P. for Norwich, and she was a cousin of Florence Nightingale. From 1865–1871 she was active with several others in advancing women's education and these efforts resulted in the founding of Girton College in 1869 and she served on the first executive committee.

The studentship has been held by famous men like A. V. Hill, John Mellanby, Sir Henry Dale, Sir John Rose Bradford and Sir Charles Sherrington, who held it for four years.

I doubt if it has ever bothered the holder of the studentship that it was founded by a woman in memory of her lover. We in the Midlands are used to eccentricities. In the group in which I work are the three towns of Coventry, Nuneaton and Rugby. In Rugby we honour William Webb Ellis because of his fine disregard for the rules of football as played in his day; in Coventry Godiva built herself an everlasting name because she rode naked in the streets; in Nuneaton one of the hospitals is named "The George Eliot" despite the fact that that woman lived in sin with a married man[1]. But let us forget her human weakness and remember her greatest gift to science, the foundation of the studentship. By it she too built herself an everlasting name.

REFERENCES

Cross, J. W., ed. (1885*a*) George Eliot's Life. London; **2**, 126.

—— (1885*b*) George Eliot's Life. London; **2**, 35.

—— (1885*c*) George Eliot's Life. London; **3**, 371.

Haight, G. S., ed. (1954–5) The George Eliot Letters. New Haven, U.S.A.; **7**, 96.

Rolleston, H. (1932) Cambridge Medical School. London; p. 84.

Trevelyan, G. M. (1945) English Social History. London; p. 563.

[1]Mr. T. B. Layton in the discussion stated that G. H. Lewes' wife bore a child to Leigh Hunt. He forgave this act of adultery but when it was repeated he left her. However as the law stood then, condoning the first adultery prevented his getting a divorce. The author thanks Mr. Layton for this information which he has found documented in the George Eliot Letters, edited by G. S. Haight.

Mr. James O. Robinson read a paper entitled **The History of Gastric Surgery** (*see Brit. J. Surg.*, 1960, in press).

Meeting
April 6, 1960

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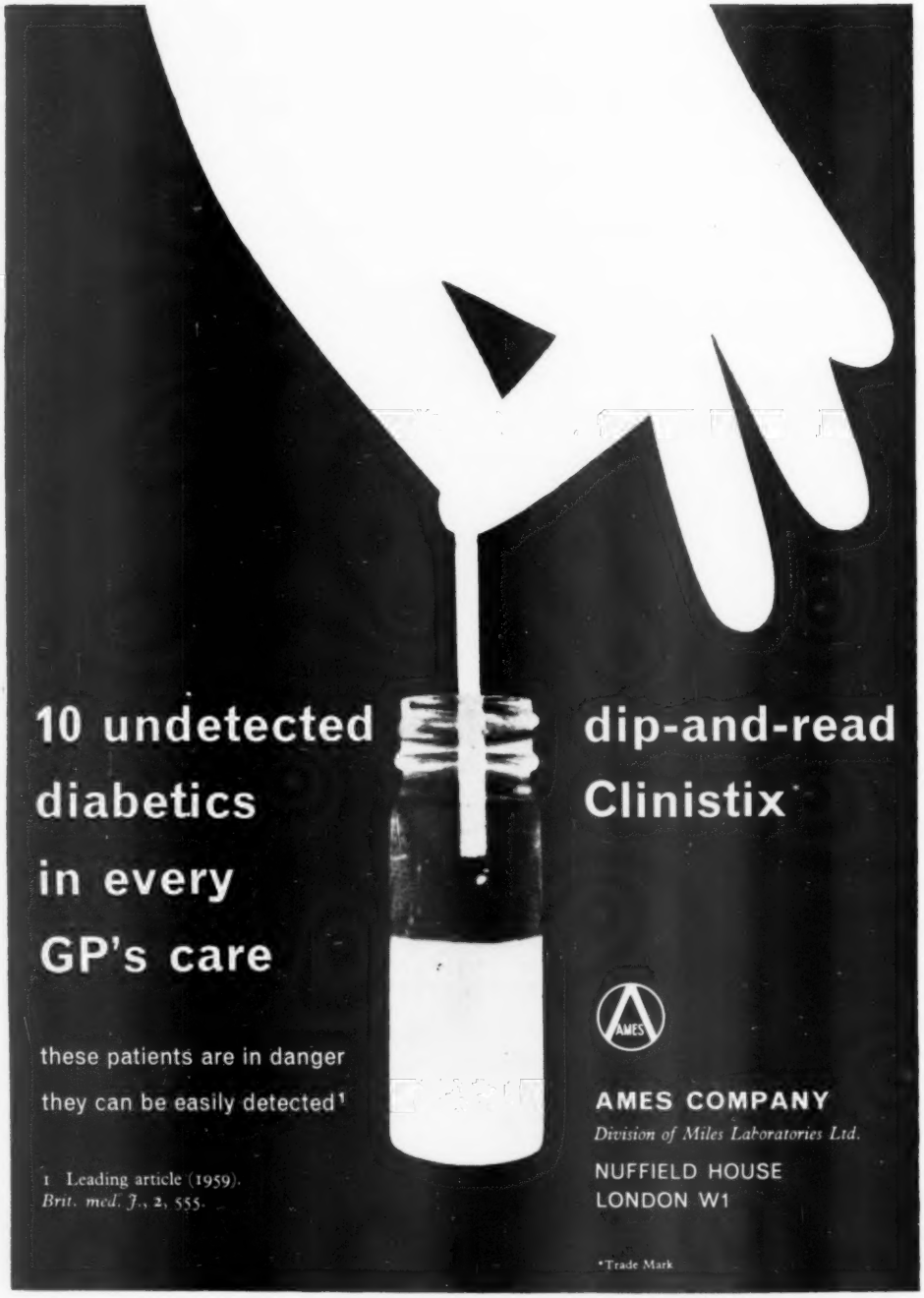
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1 Leading article (1959).
Brit. med. J., 2, 555.
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BOOK REVIEWS

Disturbances in Gastrointestinal Motility. Edited by J. Alfred Rider, M.D., Ph.D., and Hugo C. Moeller, M.D., Ph.D. (Pp. xiv + 387; illustrated. £5 4s.) Springfield, Ill.: Charles C Thomas. Oxford: Blackwell Scientific Publications. 1959.

This book is based on a programme of lectures and symposia held in the University of California in December 1958, for the purpose of "advancing basic knowledge in the field of gastrointestinal motility". Although the book does not achieve this ambitious aim, it succeeds in giving a stimulating account of some gastrointestinal disorders in terms of disordered motility. There are many distinguished names amongst the 29 contributors, but the standard of the articles varies widely and there is inevitably a good deal of repetition.

There are useful reviews of the development of methods for measuring intraluminal pressures, including the telemetering capsule, and of the motility patterns of different parts of the gastrointestinal tract and the effect of drugs. The chapters on clinical aspects of disturbances of motility are particularly interesting, e.g. "New Drugs in the Therapy of Constipation", "Infectious Diarrhœas", "Diarrhœa in the Young Child", "Acute Dilation of the Stomach and Paralytic Ileus", and the symposium on "Functional Constipation". On the other hand it is surprising that so much space has been allotted to the malabsorption syndrome, regional ileitis, and ulcerative colitis, whereas the dysphagias are dismissed in a few pages. Yet the œsophagus is the only part of the alimentary canal where recent advances in "basic knowledge" have clarified the mechanism of disorders of motility.

In one of the chapters on biliary tract disorders, the author makes a point of "the relative infrequency of postcholecystectomy syndrome in Britain as compared with elsewhere". It is therefore surprising to find that the only contribution by a British author is a long chapter on biliary dyskinesia.

Diagnostic Radioisotopes. By Charles A. Owen, Jr., M.D., Ph.D.(Med.). (Pp. xviii + 425; illustrated. £6 6s.) Springfield, Ill.: Charles C Thomas. Oxford: Blackwell Scientific Publications. 1959.

This neat short book of only 400 pages with its wide margins and extremely clear print covers the subject of the use of radioactive isotopes in clinical medicine and surgery. There is only a brief introduction to the necessary physics and it is essentially a practical book with careful details of how the various techniques may be carried out and in particular how they are at present practised at the Mayo Clinic. It is an excellent reference book for anyone starting a radioisotope department since it contains clear instructions and, in addition, good and accurate references to the literature. At six guineas the book is, however, too expensive.

Chemistry of Pancreatic Diseases. By Harris Busch, M.D., Ph.D. (Pp. xv + 160; illustrated. 42s.) Springfield, Ill.: Charles C Thomas. Oxford: Blackwell Scientific Publications. 1959.

This recent addition to the American Lecture Series is divided into three parts dealing with exocrine, endocrine and neoplastic aspects of pancreatic disease. In the first section Dr. Busch describes studies of the synthesis of pancreatic enzymes, the physiological regulation of pancreatic secretion and the drugs that influence it. The actions of the pancreatic enzymes are discussed and also diseases associated with disturbance of exocrine function. The second section is devoted to endocrine secretions of the pancreas. The discussion of the mode of action of insulin is unexpectedly brief although there is a detailed account of current views on carbohydrate metabolism. The clinical aspects of diabetes are reviewed including the biochemistry of diabetic ketosis, the use of insulin and the oral hypoglycæmic agents—sulphonamide derivatives and diguanides. Clinical hypoglycæmic syndromes are described and the remarkable statement is made that "most of the mild signs of hypoglycæmia develop in patients whose blood sugar level is approximately 75 to 85 mg/100 ml plasma". The final section is mainly an account of biochemical abnormalities of neoplastic tissue in animals.

This is an interesting and easily read little book. It provides the physician with up-to-date biochemical information about malabsorption syndromes, diabetes and neoplastic diseases.

Modern Treatment Yearbook 1960. Edited by Sir Cecil Wakeley, Bt., K.B.E., C.B. 26th annual ed. (Pp. x + 310; illustrated. 33s.) London: The Medical Press. Baillière, Tindall and Cox Ltd. 1960.

Sir Cecil Wakeley in his preface to this book writes "It is almost impossible for the busy practitioner to keep abreast of all these new advances". This is the sort of publication which makes it almost possible. The lay-out and print are pleasant and attractive and the subject matter is practical and well presented. It contains no great tracts of theoretical knowledge and erudition, but each chapter, and there are thirty-two

is well written, short, informative and interesting.

The chapter headings perhaps underline this point: "The Plastic Surgeon and the Newly Born Child" and "The Unexpected in Obstetrics" are good examples. Particularly impressive are the chapters "Infections of the Hand" and "Testicular Pain".

The illustrations are excellent but surely there is no excuse for printing positive X-ray photographs when everyone has become accustomed to negatives.

Other minor criticisms: the captions of a plain radiograph and a bronchogram have been reversed, and it seems unfortunate that in the chapter "The Prostate in General Practice" no mention is made of the Gibbon catheter, which has proved itself a most useful instrument.

This book, while obviously of great value to the keen general practitioner, should prove instructive to any doctor whose interests cover a wide range of clinical medicine.

Bibliography of Cancer Produced by Pure Chemical Compounds. A Survey of the Literature up to and Including 1947. By Otto Neubauer, M.D. (Pp. xxvii + 604. 42s.) London: Oxford University Press. 1959.

The late Professor Neubauer's bibliography was delayed by his illness; its completion by Miss Coombs is to be welcomed not only for its own sake, but also as a worthy memorial to its originator.

Some arbitrary limitations are laid down. References to colchinine and to mustard gas are omitted on the ground that those chemicals are not regarded as carcinogens; and for arsenical cancer the user is referred to the *British Journal of Cancer*, 1947, **1**, 192–251. Though space-saving must always be a consideration in a bibliography, that omission is to be regretted.

In the case of articles not in English the author index gives the title (with few exceptions) in the original language, followed by an English translation. The subject index gives translated titles only. A brief explanatory note is given in instances in which the title does not clearly show the content of a paper.

Hypnosis in Anæsthesiology. By Milton J. Marmer, M.D., M.Sc.Med.(Æs.). (Pp. xv + 150. 54s.) Springfield, Ill.: Charles C Thomas. Oxford: Blackwell Scientific Publications. 1959.

This well-written monograph is refreshingly free from the emotion and prejudice which so frequently adumbrate discussions of this subject.

A good historical review precedes a brief chapter on the psychophysiology of hypnosis; but no attempt is made to explore the profundities of the nature of the hypnotic state. After an excellent discussion of the normal psychological aspects of anæsthesia in which he stresses the importance of the anæsthetist's pre-operative visit, the author describes in great detail several techniques for the induction of hypnosis and their application to anæsthetic practice.

Much of the book is given over to the detailed description of cases, and the author's technique of combining hypnosis with small doses of narcotic drugs is not only extremely interesting, but would appear to have been remarkably successful in his hands.

Dr. Marmer writes with the authority born of experience and has not allowed his enthusiasm to overrun his common sense; he issues clear warnings on the pitfalls and limitations of hypnotic techniques, and stresses their time-consuming nature.

A good bibliography and comprehensive index complete this practical treatise which should achieve its author's purpose of inducing more anæsthetists to interest themselves in hypnosis.

A Practice of Anæsthesia. By W. D. Wylie, M.B.(Cantab.), M.R.C.P., F.F.A. R.C.S., and H. C. Churchill-Davidson, M.D. (Cantab.), F.F.A. R.C.S. (Pp. xv + 1056; 246 illustrations. 105s.) London: Lloyd-Luke (Medical Books) Ltd. 1959.

That this important new work fills a gap in the current anæsthetic literature is of secondary importance; its merits are such as to command attention at any time. It differs from other textbooks not only by assuming that the reader has some knowledge of anæsthesia, but also by approaching the subject in relation to the different physiological systems of the body.

This somewhat unorthodox approach has resulted in an eminently readable book. A wise assessment of the relevant clinical and practical problems follows naturally on every discussion of physiological principles or pathological states. The latter are considered at some length and in relation to anæsthesia in its broadest sense. The limits of present-day knowledge are clearly stated, and numerous cross-references ensure that no relevant information is overlooked.

Stress is laid on the basic principles governing the choice of anæsthetic methods, rather than on the details of techniques, but where the latter are important the authors have not hesitated to state their views.

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The price of £5 5s., though high, cannot be considered excessive for such a well-produced volume which is a credit to its publishers as well as to its authors.

Childbirth without Fear. The Principles and Practice of Natural Childbirth. By Grantly Dick-Read, M.A., M.D.(Cantab.). 4th edit. (Pp. xv + 266; illustrated. 12s. 6d.) London: William Heinemann Medical Books Ltd. 1960.

This fourth and revised edition of Grantly Dick-Read's Childbirth Without Fear has been published posthumously. It is addressed to mothers and their husbands and puts forward the author's now well-known theories of childbirth and its conduct.

Dr. Dick-Read's work has given comfort and help to thousands of mothers and it will continue long after the author's death. The medical reader may find this work unnecessarily lengthy and may consider some of it irrelevant. Dr. Dick-Read's views have been generally accepted and indeed have become an integral part of modern obstetric practice though it is sad that he still felt that his own profession did not appreciate his work.

Les Manipulations Vertébrales. By Robert Maigne. (Pp. viii + 245; illustrated. 28 NF.) Paris: Expansion Scientifique Française. 1960.

This book is divided into two parts. In the first part, the history, definition, scientific basis, indications, contraindications, effects and dangers of spinal manipulation are fully described. A most praiseworthy attempt is made to relate the rationale and effects of manipulation to sound pathological concepts. The author points out that the guarded attitude to manipulation among most doctors is due to the exaggerated claims and unacceptable rationale of osteopaths, the inexperience of many doctors practising manipulation, incomplete clinical examination, wrong diagnosis, faulty anatomical knowledge, and indiscriminate use of techniques which when correctly applied in the right patient can effect relief quicker than any other treatment. He is particularly severe on manipulations under anæsthesia.

The aims of manipulation as described in this book will surprise many—not to cause pain, and to manipulate in the direction of the free range, never into a limited and painful range; but the author argues his case reasonably and with convincing clinical examples. He believes that no one but doctors should be allowed to manipulate.

In the second part, all the techniques likely to be used in practice are fully described and amply illustrated, though it is arguable that in this realm there is no real substitute for learning directly from a master, and this section may be of more value as a reference to those with some first-hand knowledge. There is a final section on remedial exercises based on Klapp's methods.

British students in this field will welcome this sober, restrained and thoughtful contribution to a subject bristling with difficulties, though they may not accept all the indications for manipulation presented here. This book deserves to be read widely and certainly by all who manipulate their patients, or are likely to do so. Prospective readers can be reassured that school French is entirely adequate for understanding this book.

Molecular Biology. Elementary Processes of Nerve Conduction and Muscle Contraction. A symposium sponsored by Columbia University and the Rockefeller Institute; held at the Rockefeller Institute from September 25 to 30, 1958. Edited by David Nachmansohn. (Pp. xvi + 177; illustrated. $7.50) New York and London: Academic Press Inc. 1960.

Sixty-three scientists participated in the Symposium under the chairmanship of Dr. David Nachmansohn. Amongst the participants were many outstanding workers in the field of the Symposium but this volume contains only eleven of the papers. Two of them are by A. V. Hill and deal with heat production in muscle and nerve respectively. In the first, the value of heat production as an indication of chemical activity is indicated, this value lying in the ability of modern methods to localize changes in heat production to within a few milliseconds. In the second paper Hill is able by means of the extremely sensitive instruments now available to show that heat production following the passage of an impulse down a nerve is diphasic, a fall in temperature following the rise which appears to take place during the actual passage of the impulse. J. D. Robertson contributes a long and beautifully illustrated article on the electron microscopy of cell membranes of nerve fibres and their relation to the propagation and initiation of the nerve impulse. H. E. Huxley working in the same institute as the preceding two workers describes studies permitting recognition in electron micrographs of structures believed to be formed of actin and

myosin respectively. Hans Weber describes the chemical reactions occurring during contraction and relaxation of muscle while Low, Meyer, Irwin Wilson and Paolini give more chemically orientated contributions. The book is completed by two papers by Lipmann who attempts to formulate the biological use of energy in terms of chemical potentials and by Eyring who discusses the physical chemistry of nerve action.

The Essentials of Perimetry. By Howard Reed, M.B., M.S.(Lond.), F.R.C.S.(Eng.), F.R.C.S.(C.), F.A.C.S. (Pp. xi + 192; illustrated. 45s.) London: Oxford University Press. 1960.

Howard Reed based this work on a series of lectures given in London to students studying for the Diploma in Ophthalmology. It offers a simple account of field defects and its form of presentation is excellent. The technique of simplification has been taken seriously, so that the text and diagrams form a unity rarely found in medical books. Although there is nothing new in "The Essentials of Perimetry", a better introduction to the subject does not exist, and the beginner in ophthalmology should be grateful to its author. Physicians with an interest in perimetry will find all they want in this summary of principles. The illustrations are particularly striking and effective.

The Cell of Schwann. By Gilbert Causey, M.B., F.R.C.S. (Pp. x + 120; illustrated. 21s.) Edinburgh and London: E. & S. Livingstone Ltd. 1960.

Pathologists and experimentally minded neurologists as well as anatomists and embryologists will be grateful to Professor Causey for his lucid exposition of present-day knowledge of the Schwann cell. Starting with a biographical chapter on Theodor Schwann and his views on the cell which bears his name, he follows with accounts of the structure of the peripheral nerve trunk and its fibres. In these accounts Professor Causey gives a beautifully balanced summary of the leading contributions to our knowledge of these structures which have been made during the century which has followed Schwann's description of the cell he regarded as a secondary nerve cell. In these accounts we are taken up to the present day with detailed descriptions of the nerve bundles as seen with the electron microscope. Professor Causey does not hesitate to indicate the many problems still to be solved as, for example, the explanation why some Schwann cells form myelin sheaths upon the fibres they contain, while the nerve fibres in other Schwann cells remain unmyelinated. In these chapters as in the rest of the book useful though summary accounts are given of physicochemical correlations with structure.

Chapters on the ultrastructure development and tissue culture of Schwann cells, their appearance at nerve endings and the changes they undergo in degeneration and regeneration are largely illustrated by examples from the material of the author who has been a pioneer in these fields. He also draws largely on his own experience in the last chapter—on neoplasms of Schwann cells—which will be of special interest to pathologists. This little book fills an important gap in the neuro-anatomical and neuropathological literature.

Pyelonephritis. By Fletcher H. Colby, M.D. (Pp. vii + 214; illustrated. 60s.) Baltimore: The Williams & Wilkins Company. London: Baillière, Tindall & Cox Ltd. 1959.

A concise definition of pyelonephritis is not easy to give; indeed Dr. Colby does not attempt to define his subject until a quarter of the book has been read. His description of acute pyelonephritis as an active infection particularly of the interstitial tissues of the kidney is a good one and emphasizes its distinction from acute pyelitis, although the clinical difference is not always easy to establish. Acute pyelonephritis is generally curable if an organism sensitive to one of the modern chemotherapeutic or antibiotic substances is found. Failure to cure may lead to chronic pyelonephritis in which the prospect of cure is remote; the chapter on the treatment of urinary infections thus assumes great importance. Chronic pyelonephritis is not only the commonest disease of the kidney but it often has a disarming lack of symptoms until uræmia is imminent.

Among the conditions or diseases associated with or leading to pyelonephritis are listed urinary obstruction in all its forms, congenital malformations, diabetes, pregnancy, hyperparathyroidism and stone. These are also included as complicating factors in the disease, giving rise to the anomaly that "complicated" pyelonephritis has a better cure rate than uncomplicated. The view is perhaps more widely held that the so-called complicating factor is really the causative factor.

The book is so well and copiously illustrated that the appropriate illustration may be two or three pages away from its relevant text. This, however, is a minor point and the general standard of production is excellent. Dr. Colby has produced a monograph on a most important and somewhat neglected subject; it is one which should claim the attention of every branch of the medical profession.

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myosin respectively. Hans Weber describes the chemical reactions occurring during contraction and relaxation of muscle while Low, Meyer, Irwin Wilson and Paolini give more chemically orientated contributions. The book is completed by two papers by Lipmann who attempts to formulate the biological use of energy in terms of chemical potentials and by Eyring who discusses the physical chemistry of nerve action.

The Essentials of Perimetry. By Howard Reed, M.B., M.S.(Lond.), F.R.C.S.(Eng.), F.R.C.S.(C.), F.A.C.S. (Pp. xi + 192; illustrated. 45s.) London: Oxford University Press. 1960.

Howard Reed based this work on a series of lectures given in London to students studying for the Diploma in Ophthalmology. It offers a simple account of field defects and its form of presentation is excellent. The technique of simplification has been taken seriously, so that the text and diagrams form a unity rarely found in medical books. Although there is nothing new in "The Essentials of Perimetry", a better introduction to the subject does not exist, and the beginner in ophthalmology should be grateful to its author. Physicians with an interest in perimetry will find all they want in this summary of principles. The illustrations are particularly striking and effective.

The Cell of Schwann. By Gilbert Causey, M.B., F.R.C.S. (Pp. x + 120; illustrated. 21s.) Edinburgh and London: E. & S. Livingstone Ltd. 1960.

Pathologists and experimentally minded neurologists as well as anatomists and embryologists will be grateful to Professor Causey for his lucid exposition of present-day knowledge of the Schwann cell. Starting with a biographical chapter on Theodor Schwann and his views on the cell which bears his name, he follows with accounts of the structure of the peripheral nerve trunk and its fibres. In these accounts Professor Causey gives a beautifully balanced summary of the leading contributions to our knowledge of these structures which have been made during the century which has followed Schwann's description of the cell he regarded as a secondary nerve cell. In these accounts we are taken up to the present day with detailed descriptions of the nerve bundles as seen with the electron microscope. Professor Causey does not hesitate to indicate the many problems still to be solved as, for example, the explanation why some Schwann cells form myelin sheaths upon the fibres they contain, while the nerve fibres in other Schwann cells remain unmyelinated. In these chapters as in the rest of the book useful though summary accounts are given of physicochemical correlations with structure.

Chapters on the ultrastructure development and tissue culture of Schwann cells, their appearance at nerve endings and the changes they undergo in degeneration and regeneration are largely illustrated by examples from the material of the author who has been a pioneer in these fields. He also draws largely on his own experience in the last chapter—on neoplasms of Schwann cells—which will be of special interest to pathologists. This little book fills an important gap in the neuro-anatomical and neuropathological literature.

Pyelonephritis. By Fletcher H. Colby, M.D. (Pp. vii + 214; illustrated. 60s.) Baltimore: The Williams & Wilkins Company. London: Baillière, Tindall & Cox Ltd. 1959.

A concise definition of pyelonephritis is not easy to give; indeed Dr. Colby does not attempt to define his subject until a quarter of the book has been read. His description of acute pyelonephritis as an active infection particularly of the interstitial tissues of the kidney is a good one and emphasizes its distinction from acute pyelitis, although the clinical difference is not always easy to establish. Acute pyelonephritis is generally curable if an organism sensitive to one of the modern chemotherapeutic or antibiotic substances is found. Failure to cure may lead to chronic pyelonephritis in which the prospect of cure is remote; the chapter on the treatment of urinary infections thus assumes great importance. Chronic pyelonephritis is not only the commonest disease of the kidney but it often has a disarming lack of symptoms until uræmia is imminent.

Among the conditions or diseases associated with or leading to pyelonephritis are listed urinary obstruction in all its forms, congenital malformations, diabetes, pregnancy, hyperparathyroidism and stone. These are also included as complicating factors in the disease, giving rise to the anomaly that "complicated" pyelonephritis has a better cure rate than uncomplicated. The view is perhaps more widely held that the so-called complicating factor is really the causative factor.

The book is so well and copiously illustrated that the appropriate illustration may be two or three pages away from its relevant text. This, however, is a minor point and the general standard of production is excellent. Dr. Colby has produced a monograph on a most important and somewhat neglected subject; it is one which should claim the attention of every branch of the medical profession.

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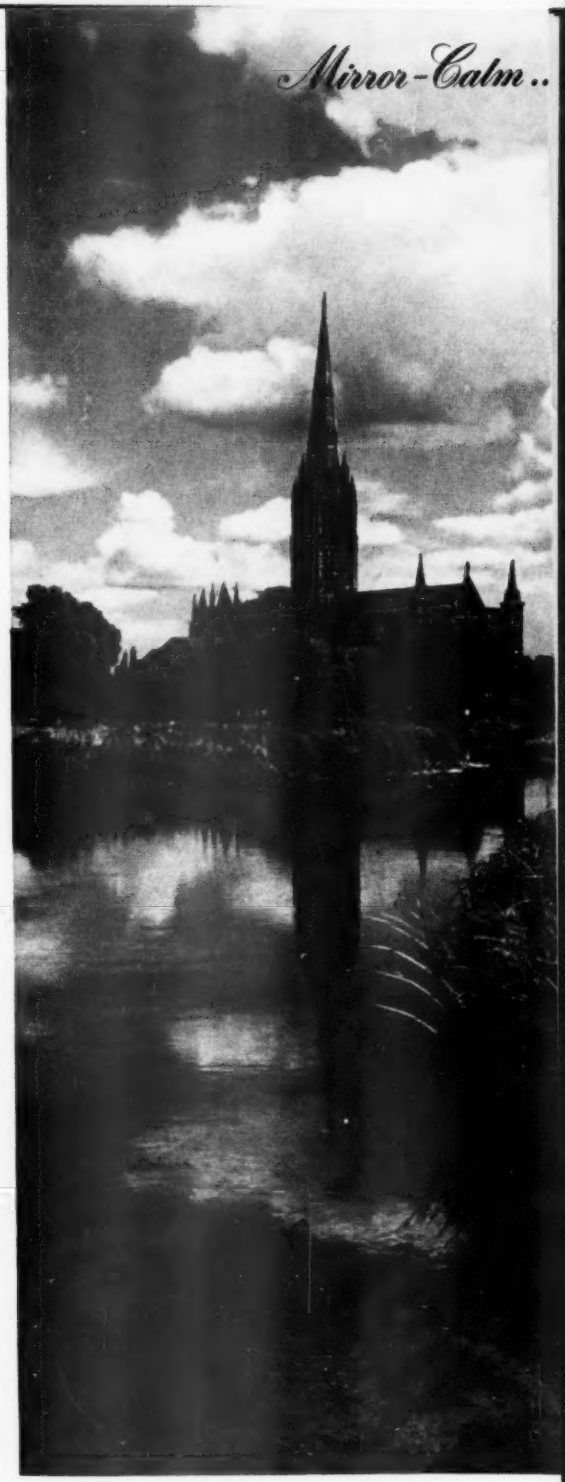

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